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BRONCHOSCOPIC ASPECTS OF ASTHMA IN CHILDREN

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Notwithstanding the tremendous amount of research that has been conducted in recent years on the subject of chronic allergic asthma, the precise pathologic physiology of the disease still continues to defy adequate explanation. Extensive postmortem studies [1] made after fatal attacks have disclosed rather characteristic changes in the tissue, comprising hyalinization and thickening of the basement membrane of the bronchi, hyperplasia of the mucus-secreting cells, varying quantities of viscid mucoid material in the air passages, eosinophilic infiltration and edema of the bronchial wall, hypertrophy of the bronchial musculature and variable degrees of pulmonary emphysema. In a large number of autopsies performed on asthmatic patients who have died of an intercurrent disease, however, such changes have not been found, suggesting that they probably represent merely the picture of excessively violent

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1. (*a*) Huber, H. L., and Koessler, K. K.: Pathology of Bronchial Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922. (*b*) Rackemann, F. M.: Fatal Asthma: Report of a Case with Autopsy, Boston M. & S. J. **194**:531 (March 25) 1926. (*c*) Kountz, W. B., and Alexander, H. L.: Death from Bronchial Asthma: Report of Three Cases, Arch. Path. **5**:1003 (June) 1928. (*d*) Steinberg, B., and Figley, K. D.: Pathology of Asthma: Nonbacterial Allergic and Bacterial Types Based on Autopsy Material, J. Lab. & Clin. Med. **13**:921 (July) 1928. (*e*) Harkavy, J.: Observations on Fatal Bronchial Asthma: A Report of Two Cases, J. Allergy **1**:136 (Jan.) 1930. (*f*) Wright, C. B.: Death from Bronchial Asthma, J. A. M. A. **94**:1218 (April 19) 1930. (*g*) Macdonald, I. G.: The Local and Constitutional Pathology of Bronchial Asthma, Ann. Int. Med. **6**:253 (Aug.) 1932. (*h*) Steinberg, B.: Recognition of the Allergic State by Tissue Examination: the Respiratory Tract and the Nasal Sinuses, Am. J. Clin. Path. **4**:169 (March) 1934. (*i*) Waldbott, G. L.: Pathologic Changes in Asthmatic Infants, Am. J. Dis. Child. **49**:1531 (June) 1935. (*j*) Michael, P. P., and Rowe, A. H.: Pathology of Two Fatal Cases of Bronchial Asthma, J. Allergy **6**:150 (Jan.) 1935.

exacerbation rather than that of the underlying morbid process in its truly chronic state. According to Thieme and Sheldon,[2] the only constant structural modification in long-standing asthma is hyaline thickening of the bronchial basement membrane. Attempts to correlate the pathologic data with results of clinical and roentgenographic investigation [3] have thus far failed to produce any unanimity of opinion regarding the actual mechanism of the asthmatic paroxysm. The development of episodic wheezing and respiratory distress is commonly attributed to spasm of the bronchial muscles,[3d] to swelling of the bronchial mucous membrane consequent to intramural exudation,[4] to occlusion of the bronchial lumen by secretory products [5] or to a combination of these phenomena, but there is little agreement as to the relative importance of the factors concerned.

During the past few years we have had the opportunity of observing a great many asthmatic children bronchoscopically. In view of the fact that bronchoscopy has come to be recognized as a procedure of prime importance in the study of respiratory disease, we thought that an account of our observations on these children and a comparison of our observations with those recorded by other investigators might be of value in adding to our understanding of allergic asthma and its manifestations. We therefore selected 100 representative cases for detailed analysis. In every case the allergic nature of the condition was indicated by definite cutaneous sensitivity to specific allergens. In each case bronchoscopy was performed without anesthesia at least two times. The youngest patient at the time of his initial bronchoscopy was 1 year of age, and the oldest 13 years. The age at which the asthmatic symptoms had their onset varied from 3 months to 12 years, and the duration of the symp-

2. Thieme, E. T., and Sheldon, J. M.: A Correlation of the Clinical and Pathological Findings in Bronchial Asthma, J. Allergy **9**:246 (March) 1938.

3. (*a*) Smith, W. O.: Bronchial Asthma: Clinical Studies and Observations in Three Hundred and Fourteen Cases, Arch. Otolaryng. **15**:165 (Feb.) 1932. (*b*) Christopherson, J. B.: The Anatomy of Chronic Bronchitis and Bronchial Asthma as Disclosed by Lipiodol Examination, Am. J. M. Sc. **186**:504 (Oct.) 1933. (*c*) Hurtado, A., and Kaltreider, N. L.: Studies of Total Pulmonary Capacity and Its Subdivisions: Observations During the Acute Respiratory Distress of Bronchial Asthma and Following the Administration of Epinephrine, J. Clin. Investigation **13**:1053 (Nov.) 1934. (*d*) Rigler, L. G., and Koucky, R.: Pathologic Physiology of Bronchial Asthma, Am. J. Roentgenol. **39**:353 (March) 1938. (*e*) Barach, A. L., and Swenson, P.: Effect of Breathing Gases Under Positive Pressure on Lumens of Small and Medium-Sized Bronchi, Arch. Int. Med. **63**:946 (May) 1939. (*f*) Ratner, B.: Experimental Asthma, Am. J. Dis. Child. **58**:699 (Oct.) 1939.

4. Ramirez, M. A.: Bronchial Asthma and Nasal Allergy, Arch. Otolaryng. **28**:199 (Aug.) 1938.

5. Steinberg, B.: The Mechanism of an Acute Asthmatic Attack in Chronic Allergic Asthma, J. Allergy **3**:139 (Jan.) 1932.

toms at the time of the first endoscopic examination ranged from one month to ten years. Most of our observations were made in the intervals between acute attacks, direct inspection of the tracheobronchial tree during the actual paroxysm being confined to those children whose respiratory discomfort could not be relieved by ordinary pharmaceutic means.

The majority of the children in our group suffered from frequently recurring colds, and many had clinical signs of chronic paranasal sinusitis. A persistent cough was present in 27. Of 40 children whose sinuses were examined with roentgen rays, the existence of disease was manifest roentgenographically in 35. It is not surprising, therefore, that nonspecific inflammatory changes should occupy a prominent place in the bronchoscopic picture, as illustrated by the figures in table 1. In only 9 patients were the carina and the bronchial spurs normally sharp and the mucous membrane normal in color at every examination. The high

TABLE 1.—*Abnormal Bronchoscopic Features in One Hundred Asthmatic Children*

Nature of Abnormality	Number of Children in Whom Abnormality Was Found
Congestion of mucous membrane	78
Mucopurulent or thick mucoid secretion	60
Accentuation of expiratory narrowing of lumen	36
Widening of bronchial spurs	22
Thickening of mucous membrane	18
Frank pus	15
Widening of carina	12

incidence of chronic infection of the respiratory tract in this group of children with asthma was similar to that noted by Rackemann,[6] Chobot [7] and others.[8] Crump [9] has called attention to the fact that purulent tracheobronchitis occurs with much greater frequency in asthmatic children than it does in asthmatic adults.

6. Rackemann, F. M.: The Use of Drugs in Asthma, J. A. M. A. **114**:1998 (May 18) 1940.

7. Chobot, R.: Asthma in Children: An Analysis of Eighty-Four Cases, Am. J. Dis. Child. **45**:25 (Jan.) 1933.

8. (*a*) Jackson, C., and Jackson, C. L.: Bronchoscopy, Esophagoscopy and Gastroscopy, Philadelphia, W. B. Saunders Company, 1934, p. 320. (*b*) Cooke, R. A.: Asthma in Children: Its Causes and Treatment, J. A. M. A. **102**:664 (March 3) 1934. (*c*) Kelley, S. F.: The Incidence of Sinusitis and Nasal Polypi in Bronchial Asthma, Laryngoscope **46**:692 (Sept.) 1936. (*d*) Creasy, R. C.: The Role That Surgery of the Paranasal Sinuses Plays in the Asthmatic Child, ibid. **48**:415 (June) 1938. (*e*) Pratt, H. N.: The Pathologic Physiology of Bronchial Asthma, with Reference to the Role of Infection, New England J. Med. **223**:626 (Oct. 17) 1940.

9. Crump, J.: Asthma in Children Treated with Autogenous (Bronchoscopic) Vaccine, Am. J. Dis. Child. **58**:768 (Oct.) 1939.

Aside from the signs of chronic inflammatory disease, the tracheas and the bronchi of these children presented no distinctive endoscopic appearance. Although the deep red or purple mucous membrane looked somewhat turgid at times, as a result of the extreme vascular engorgement, there was no evidence of mucosal edema comparable to that seen in the nose in patients with allergic rhinitis; in the patients whose tracheobronchial mucous membrane appeared chronically thickened, the thickening was not appreciably increased during the paroxysm, nor was there evidence of bronchospasm or organic bronchostenosis. Our failure to detect any suggestion of spasm in the bronchi accessible to direct visualization coincides with that reported by Jackson,[10] Clerf [11] and all other investigators who have described their bronchoscopic observations. The absence of bronchial strictures in the group of patients studied by us, on the other hand, is strikingly at variance with the experience of Prickman and Moersch,[12] who have found one or more bronchi to be definitely reduced in caliber in a large proportion of their asthmatic patients.

It will be noted that 36 per cent of the children in our series showed some accentuation of the physiologic posteroanterior narrowing that occurs in the trachea and the larger bronchi during expiration and cough. This accentuation, which has been cited by Lukens,[13] Clerf [14] and others as a common observation in asthma, varied considerably in degree in different children and was far from constant in each child, not infrequently being very marked at one examination and only moderate or even entirely absent at a subsequent bronchoscopy. Its incidence was no greater in the children examined during acute episodes than it was in the group as a whole. When it was most severe the membranous posterior wall of the air passage moved so far forward that virtually complete collapse of the lumen was produced and the opening converted into a crescentic slit; if, in addition, the lateral walls moved inward, as they did rather frequently, the lumen became a tiny triangle or assumed the shape of an inverted V. Even in instances in which the tussive narrowing was extremely pronounced, however, the tracheal and bron-

10. Jackson, C.: Wheezing Respiration in Children: Bronchoscopic Observations on Stridorous and Asthmatoid Breathing, Am. J. Dis. Child. **41**:153 (Jan.) 1931.

11. Clerf, L. H.: Bronchoscopy as an Aid in Diagnosis and Treatment of Bronchial Asthma, J. A. M. A. **89**:872 (Sept. 10) 1927.

12. Prickman, L. E., and Moersch, H. J.: (*a*) Asthma and Its Association with Bronchostenosis, M. Clin. North America **23**:961 (July) 1931; (*b*) Bronchostenosis Complicating Allergic and Infectious Asthma, Ann. Int. Med. **14**:387 (Sept.) 1940.

13. Lukens, R. M.: Bronchoscopy in the Treatment of Asthma, Laryngoscope **35**:227 (March) 1925.

14. Clerf, L. H.: The Present Status of Bronchoscopy in Bronchial Asthma, Ann. Int. Med. **9**:1050 (Feb.) 1936.

chial lumens always resumed their normal contours and diameters on inspiration. The frequency of occurrence of exaggerated expiratory narrowing of the airway bore no relation to the patient's age at the onset of his symptoms or to his age at the time of his first bronchoscopic examination, but it appeared to be directly proportional to the brevity of the asthmatic history. The phenomenon was observed in 60 per cent of those in whom the duration of the asthma was less than one year, in 30 per cent of those in whom it was one to five years and in only 22 per cent of those in whom it was longer than five years.

In 60 children whose bronchi were found to contain mucopurulent or thick mucoid material the quantity varied from a drop or two to several cubic centimeters. When the suppurative element was lacking, the secretion was white or light gray, extremely thick and viscid and almost mucilaginous in consistency at times and clung tenaciously to the walls of the trachea and the bronchi. Often a line of stringy mucus extended across the bronchial lumen from one wall to the other. In spite of the tendency of the exudate to adhere firmly to the bronchial wall, the mucosal surface was invariably seen to be smooth and flat after the tenacious material had been removed by suction. The frequency of endobronchial exudation of thick mucoid material bore no discernible relation to the patient's age at the onset of his symptoms, to his age at the time of his first bronchoscopic examination or to the length of his asthmatic history. Weille [15] has described the presence of viscid secretion as the most typical endoscopic feature of an asthmatic paroxysm. In our series it was found in every child who was examined bronchoscopically in the midst of the acute attack. In every instance the respiratory distress was unmistakably diminished in severity after aspiration of the secretion; in some cases it subsided completely.

In 97 children from whom specimens could be obtained bronchoscopically the bronchial exudate was studied bacteriologically by direct smears and by aerobic and anaerobic cultures. The results, shown in table 2, corroborate the observations of Stevens,[16] Crump [9] and others [17] that patients with asthma do not have a uniform bacterial flora. Not only was there extreme variation among the different children in our group, but the bacterial contents of material aspirated at successive

15. Weille, F. L.: Studies in Asthma: Bronchoscopy in Asthma, New England J. Med. **205**:848 (Oct. 29) 1931.

16. Stevens, F. A.: The Treatment of Infectional Asthma in Children with Filtrates of Cultures of Upper Respiratory Pathogenic Bacteria, J. Pediat. **14**:307 (March) 1939.

17. (*a*) Walker, I. C., and Adkinson, J.: Bacteriologic Examination of Seven Hundred and Twenty-Four Sputums from as Many Patients with Bronchial Asthma, Arch. Int. Med. **41**:601 (April) 1928. (*b*) Wilmer, H. B., and Cobe, H. M.: Vaccine Therapy: The Uses and Misuses; a Statistical Bacteriologic Study, J. Allergy **4**:414 (July) 1933.

bronchoscopies on the same patient were rarely alike. No fungi or tubercle bacilli were recovered from the bronchi of any of our patients.

Despite the presence of a thick endobronchial exudate, complete occlusion of a bronchus with consequent lobar or segmental atelectasis as demonstrated by roentgenography was not apparent in any of our children. This suggests that the incidence of localized pulmonary collapse is not unduly high in asthmatic persons but corresponds rather closely to that obtaining in the general population. The coexistence of asthma and atelectasis has been cited by various authors [18] in isolated case reports, but the literature does not contain any comprehensive data on which to base an accurate estimation of the actual frequency with which the two disease processes are associated.

A good deal has been written about the supposed pathogenetic relation between allergic tracheobronchial disease and the development of

TABLE 2.—*Presence of Bacteria in Specimens of Bronchial Secretion Obtained Endoscopically in Ninety-Seven Asthmatic Children*

Micro-Organism	Number of Children in Whom Micro-Organism Was Found
Micrococcus catarrhalis	64
Nonhemolytic streptococcus	43
Pneumococcus	42
Nonhemolytic staphylococcus	38
Hemolytic streptococcus	31
Bacillus influenzae	7
Hemolytic staphylococcus	5
Neisseria sicca	5
Bacillus fusiformis	2
Bacteroid	2
Diphtheroid	1

bronchial dilatations, conveying the impression that the inflammatory changes and the bronchial obstruction accompanying chronic asthma are frequently precursors of bronchiectasis. Yet ectasia of the bronchi has not been found to be especially common in asthmatic patients examined at autopsy. Nor was it a prominent feature of the clinical picture in our group of asthmatic children. Of those who exhibited symptoms suggesting the existence of bronchiectasis, bronchographic study was carried out on 20. Ectatic bronchi were outlined in 5 and normal-sized bronchi in the remainder.

18. (*a*) Clarke, J. A., Jr.: Pulmonary Atelectasis as a Complication of Bronchial Asthma, Arch. Int. Med. **45**:624 (April) 1930. (*b*) Wilmer, H. B.; Cobe, H. M., and Lee, W. E.: The Incidence of Allergy and Asthma in a Group Developing Post-Operative Atelectasis, Ann. Surg. **91**:651 (May) 1930. (*c*) Peshkin, M. M., and Fineman, A. H.: Acute Massive Atelectasis and Asthma, Am. J. Dis. Child. **42**:590 (Sept.) 1931. (*d*) Friedman, T. B., and Molony, C. J.: Role of Allergy in Atelectasis in Children, ibid. **58**:237 (Aug.) 1939.

COMMENT

Several logical deductions regarding the pathologic physiology of allergic asthma may, we believe, be made on the basis of our endoscopic studies. In the first place, our bronchoscopic observations offer no support whatever for the theory of a bronchospastic origin of the wheezing and dyspnea and lead us to question the validity of that concept. True, the bronchoscopist cannot explore the tiny peripheral bronchi and bronchioles, and his opinion of conditions prevalent therein must of necessity be based solely on inference; but, as Jackson [10] has pointed out, spasmodic contraction of minute bronchial subdivisions is hardly compatible with the production of a wheeze audible at the open mouth. It is not inconceivable that expiratory collapse of the bronchial lumen might be responsible for the characteristic symptoms in a limited number of patients, but the irregularity of occurrence of this phenomenon precludes our accepting it as an explanation for the usual acute attack. Likewise, bronchoedema is far too uncommon to merit serious consideration as a basic asthmogenic factor. In the light of present knowledge it seems likely that the presence of thick mucoid secretion in the trachea and in the bronchi is intimately related to the creation of the respiratory dysfunction. Its exact role, however, is difficult to appraise, for when one considers the comparative rarity with which asthmatic manifestations are encountered in bronchiectatic patients who have copious endobronchial exudation,[19] one cannot but feel that precipitation of an attack of asthma must entail the operation of some other mechanical element in addition to mere bronchial occlusion caused by inspissated secretion.

No matter what the correct explanation for the paroxysms of dyspnea may be, there can be no question that bronchoscopy has a definite place in the management of patients with allergic asthma. Its diagnostic indications are epitomized in Jackson's classic statement "All is not asthma that wheezes." Positive reactions to cutaneous tests for sensitivity to specific allergens do not rule out the presence of an aspirated foreign body, compression of the airway by enlarged mediastinal glands or other obstruent tracheobronchopathy. Therapeutically, bronchoscopy is indicated in every case in which removal of tracheobronchial exudate will afford the patient symptomatic relief. It should be performed without hesitation whenever an asthmatic attack is resistant to control by the commonly employed alleviative measures.

SUMMARY

A group of 100 children with chronic allergic asthma was studied bronchoscopically. No evidence of bronchospasm or bronchoedema was

19. Diamond, S., and Van Loon, E. L.: Bronchiectasis in Childhood, J. A. M. A. **118**:771 (March 7) 1942.

seen in any of the patients. Nonspecific inflammatory changes were present in 91. Accentuation of the physiologic expiratory narrowing occurred in 36. Mucopurulent or thick mucoid secretion was found in 60. There was no characteristic bacteriologic picture. Lobar or segmental atelectasis was not observed in any of the children. Of 20 patients on whom bronchography was done, 5 were shown to have bronchiectasis. The only constant feature of the endoscopic appearance in children examined in the course of an acute attack was the presence of thick, viscid intraluminal secretion.

COMBINED IMMUNIZATION OF INFANTS AGAINST DIPHTHERIA, TETANUS AND WHOOPING COUGH

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Prophylaxis against diphtheria is universally recommended; prophylaxis against whooping cough is now generally accepted; and prophylaxis against tetanus has been found effective, although it has not been used routinely. The combined prophylaxis against two of the three diseases—diphtheria and tetanus—has been in use for several years.[1] This paper records my experience with the combined prophylaxis against the three diseases—diphtheria, tetanus and whooping cough.

Theoretically, this triple immunization would present two advantages: first, possible adsorption of the toxoids and toxins by bacterial suspension, thus affording what Ramon [2] has called a larger "effective antigenic surface;" second, nonspecific enhancement of antigen production, termed by Ramon "antigenic synergy." As an example of antigenic enhancement produced by the mixture of a toxoid with a bacterial vaccine, the work of Schütze [3] is of interest. He immunized guinea pigs with mixtures of alum-precipitated diphtheria toxoid and whooping cough vaccine and reported the antigenic efficiency against diphtheria to be increased greatly while the antigenic efficiency against whooping cough was not changed.

In this paper, for reasons detailed later, immunization against three diseases—diphtheria, tetanus and whooping cough—was performed with

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From the Pediatric Service of the Bronx Hospital, Dr. B. S. Denzer, Director.

Dr. J. R. Fried, of the Bronx Hospital, gave technical assistance in the withdrawal of blood samples; Dr. H. M. Powell, of the Lilly Research Laboratory, made the complement fixation, agglutination and mouse protection tests, and Mr. F. G. Jones, of the Lilly Research Laboratory, made the diphtheria and tetanus antitoxin determinations.

1. (*a*) Jones, F. G., and Moss, J. M.: Antitoxic Titers of Human Subjects Following Immunization with Combined Diphtheria and Tetanus Toxoids, Alum-Precipitated, J. Immunol. **33**:173 (Sept.) 1937; (*b*) Combined Diphtheria Toxoid and Tetanus Toxoid, Alum Precipitated, J. Lab. & Clin. Med. **24**:512 (Feb.) 1939. (*c*) Bigler, J. A., and Werner, M.: Active Immunization Against Tetanus and Diphtheria in Infants and Children, J. A. M. A. **116**:2355 (May 24) 1941.

2. Ramon, G.: Mixed Vaccinations, Internat. Clin. **1**:241 (March) 1939.

3. Schütze, H.: Simultaneous Immunization Against Whooping Cough and Diphtheria, Lancet **2**:192 (Aug. 17) 1940.

mixtures of the following antigens: clear diphtheria toxoid, alum-precipitated tetanus toxoid, whooping cough vaccine and whooping cough toxin. Table 1 illustrates the doses and intervals. The following are the materials used and the methods of preparation:

1. Clear diphtheria toxoid: Standard preparation of the New York City Department of Health.

2. Alum-precipitated tetanus toxoid: In most cases Eli Lilly & Co. preparation was used; a few persons were immunized with Squibb's alum toxoid, of which the dose is 1 cc.

3. Whooping cough vaccine: Either the Sauer type or the pertussis vaccine prepared by Eli Lilly & Co., in concentration of 20 billion organisms to the cubic centimeter.

4. Whooping cough toxin: This was prepared by my modification of the method for growth of Haemophilus pertussis in liquid mediums suggested by Wildtgrube.[4] One part of fresh human whole blood was laked in two parts of

TABLE 1.—*Dosage Schedule*

Injections	Diphtheria Toxoid, Clear, Cc.	Tetanus Toxoid, Alum Precipitated, Cc.	Whooping Cough Vaccine, Number of Organisms	Whooping Cough Toxin, Cc.
First month	...	0.5	20 billions	0.1
Second month	1.0	...	20 billions	0.1
Third month	...	0.5	20 billions	0.1
Fourth month	1.0	...	20 billions	0.1
Fifth month	0.5	0.5	20 billions	0.1

At the eighth month a Schick test and a blood test were made.

distilled water, inoculated heavily with a seventy-two hour, phase 1, virulent H. pertussis culture from a human blood–Bordet-Gengou medium, and transferred to an Erlenmeyer flask of such a size that the depth of the liquid medium was no more than 1 cm. The liquid blood culture was incubated at 37 C., for one week, run through a ball mill to destroy the bodies of the bacteria, and submitted to Berkefeld filtration. After sterility tests were completed, the material was allowed to stand at room temperature for approximately four weeks, to complete the destruction of the thermolabile toxin.

Toxin prepared like this whooping cough toxin contains the endotoxin and the thermostable exotoxin. The standardization of these toxins is admittedly unsatisfactory, and the evidence concerning their antigenic value is controversial. Thus Flosdorf, Dozois and Kimball,[5] as well as others, found that separation of these toxins is not feasible. Both Sauer and Mishulow sought to enhance the antigenic value of their vaccines

4. Wildtgrube, F.: Zusammenfassung neuerer Erkenntnisse über Ätiologie und Pathogenese des Keuchhustens, Ergebn. d. inn. Med. u. Kinderh. **45**:643, 1933.

5. Flosdorf, E. W.; Dozois, T. F., and Kimball, A. C.: Studies with H. Pertussis, J. Bact. **41**:457 (April) 1941.

by maintaining or increasing their toxin content. Sauer[6] in the preparation of his vaccine insisted on using the unwashed organisms because of their presumed exotoxic content. Mishulow[7] reenforced her vaccine with a pertussis toxic filtrate and after using this preparation found the agglutination titer increased in a higher percentage of children than with Sauer vaccine. Weichsel, Cohen and I,[8] in a comparison of this toxin vaccine and Sauer vaccine, reported positive complement fixation reactions in a higher percentage of children with the toxin vaccine than with Sauer vaccine. (Park[9] secured good clinical results in prophylaxis with this toxin vaccine, but in general it has not found favor clinically.)

It seemed worth while in choosing a pertussis vaccine to seek a substance that presented the highest antigenic potency, even though this superiority is based only on serologic evidence. This evidently was the objective of Sauer and Mishulow, as indicated above. For this reason, the vaccine reenforced with toxin was chosen for this study. Although, as has already been indicated, standardization is unsatisfactory, preliminary injection of the toxin alone was done. Intracutaneous injection of 0.1 cc. of the toxin used by me into human beings caused a slight erythema; intramuscular injection in doses as high as 5 cc. produced a local reaction 1 inch in diameter, which subsided in twenty-four hours.

MATERIAL

The children were referred to the special clinic by the hospital infant hygiene clinic and by local social service agencies. Seventy-eight well children, from 6 to 9 months of age, who had never been seriously or acutely ill and had never been subjected to any immunization procedures, were given injections at monthly intervals, according to the schedule shown in table 1. Distribution according to color was 77 white and 1 Negro; according to sex, 38 male and 40 female. All were clinic patients; all were given an injection by me every four weeks for a total of five injections. The mothers were given mimeographed direction sheets and were instructed in how to take and record the rectal temperatures of the children three times a day for the forty-eight hour period following each injection.

The toxoid, vaccine and toxin were withdrawn into the same syringe, thoroughly shaken and injected intramuscularly into an area of the upper part of the arm washed with alcohol. Three months after the completion of the fifth injection, a Schick test was done and blood was withdrawn for serum titrations.

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6. Sauer, L., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1941, vol. 2, chap. 34, p. 15.

7. Mishulow, L.: Comparative Study of Agglutinin Response After Pertussis Vaccination with Sauer Vaccine and with Toxin Vaccine and in Untreated Clinical Pertussis, J. Pediat. **9**:492 (Oct.) 1936.

8. Lapin, J. H.; Cohen, P., and Weichsel, M.: Prophylactic Vaccination Against Whooping Cough, Arch. Pediat. **56**:590 (Sept.) 1939.

9. Park., W. H., and others: Round Table Discussion on Whooping Cough, J. Pediat. **7**:690 (Nov.) 1935. Park, W. H.: Pertussis Prophylactic Vaccination, Second Internat. Cong. Microbiol., 1937, sect. 8, p. 487.

RESULTS

Unfavorable Reactions.—Three hundred and eighty injections were given to the 78 children. It was necessary to discontinue immunization in the case of only 1 child, who presented a typical alum cold abscess after the first injection. Local reactions showing some swelling and slight induration of about 2 inches (5 cm.) in diameter were noted in 50 per cent of the subjects. Cold compresses were used to relieve local discomfort. Temperature was noted as indicated in table 2.

Contrary to the experiences of others with older subjects,[10] no allergic reactions were noted.

Serum Titrations.—The serum titrations employed were as follows:

1. The diphtheria antitoxic titer in the blood serum was estimated by Jones and Moss's [1a] modification of Fraser's intracutaneous test on rabbits.

TABLE 2.—*Summary of Temperature Readings Made After Injections*

Injection	No Fever	101 F.	102 F.	103 F.
First	46.1%	33.3%	15.4%	5.2%
Second	56.4%	19.2%	17.9%	6.5%
Third	75.3%	12.3%	8.2%	4.2%
Fourth	80.3%	3.3%	10.6%	6.8%
Fifth	92.0%	1.5%	0.0%	1.5%

2. The tetanus antitoxic titer in the blood serum was estimated by Jones and Moss's [1b] modification of the standard guinea pig test.

3. Pertussis agglutination was judged by the rapid agglutination test [11] and recorded as from negative to 4 plus.

4. Pertussis complement fixation was estimated by the method of Powell and Jamieson.[12]

5. Pertussis intraperitoneal mouse protection tests were done by the method of Powell and Jamieson.[13]

Results of serum titrations are embodied in table 3.

10. Cooke, R. A.; Hampton, S. F., and others: Allergy Induced by Immunization with Tetanus Toxoid, J. A. M. A. **114**:1854 (May 11) 1940. Parish, H. J., and Oakley, C. L.: Anaphylaxis After Injection of Tetanus Toxoid, Brit. M. J. **1**:294 (Feb. 24) 1940. Whittingham, H. E.: Anaphylaxis Following Administration of Tetanus Toxoid, ibid. **1**:292 (Feb. 24) 1940. Cunningham, A. A.: Anaphylaxis After Injection of Tetanus Toxoid, ibid. **2**:522 (Oct. 19) 1940.

11. Powell, H. M., and Jamieson, W. A.: A Rapid Pertussis Agglutination Test, to be published.

12. Powell, H. M., and Jamieson, W. A.: Laboratory Assay of Undenatured Bacterial Antigen, J. Immunol. **36**:361 (May) 1939.

13. Powell, H. M., and Jamieson, W. A.: Further Studies on the Immunology of Hemophilus Pertussis, J. Immunol. **32**:153 (Feb.) 1937.

Immunity Against Diphtheria.—This has been judged, first, by the reaction to the Schick test and, second, by the level of diphtheria antitoxin in the blood. One hundred per cent of the children inoculated in this series had a negative Schick reaction, as compared with the generally accepted figure of 90 to 95 per cent for the usual three monthly doses of clear toxoid. While the Schick test, from a practical viewpoint, is an almost perfect indicator of immunity to diphtheria, authorities [14] agree on limitations, which interfere with the use of the Schick test in determining the comparative antigenicity of various methods of prophylaxis. For this reason, titration of the levels of diphtheria antitoxin in the blood affords a better method for comparison.

The diphtheria antitoxic level in the blood of 29 of the 32 children in this study was 0.1 + unit, definitely lower then Fraser's [15] estimate of 0.3 unit as the average level for his group of 244 children. Since

TABLE 3.—*Results of Serum Titrations for Diphtheria*

Author	Months After 3 Doses of Toxoid	Schick Test Given Before	Age	No. of Children	Percentage of Subjects with Antitoxin Level * of: <1/250	>1/250 <1/100	>1/100 <1/50	>1/50 <1/10	>1/10 <1/2	>1/2 <10
Fraser and Halpern: Canad. Pub. Health J. **26**: 476, 1935	3	Yes	Preschool	36	..	5	3	14	53	25
Combined immunization (Lapin)	3	No	Infants	32	3	..	6	..	91	

* The antitoxic level diphtheria antitoxin titrations were made on all serum samples at the following levels: 0.002, 0.005, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, and 10.0 units.

all of Fraser's group were given a Schick test before immunization, it is possible that the subsequent immunization injection may have acted as a "boosting" dose. Another cause of this seeming inferiority in antitoxic levels in my series may be the fact that 64 per cent of the children were below 9 months of age at the beginning of the combined immunization; it has long been recognized that such young children, who still retain passive immunity from their mothers, are poor antitoxin producers.[16] On the other hand, further analysis of the figures in table 3 shows certain distinct advantages of the combined immunization: First,

14. Taylor, E. M., and Moloney, P. J.: An Investigation of the League of Nations Standard Requirements for Schick Toxin, J. Immunol. **33**:191 (Sept.) 1937. Fitzgerald, J. G.; Fraser, D. T.; McKinnon, N. E., and Ross, M. A.: The Specific Prevention of Diphtheria, Bull. New York Acad. Med. **14**:568 (Sept.) 1938.

15. Fraser, D. T.: Diphtheria Toxoid: Review, Canad. Pub. Health J. **30**:469 (Oct.) 1939.

16. Zinsser, H.; Enders, J. F., and Fothergill, L. D.: Immunity: Principles and Application in Medicine and Public Health, ed. 5, New York, The Macmillan Company, 1939, p. 531.

100 per cent of the children had negative Schick reactions at the end of three months; second, 97 per cent had more than 1/250 unit of antitoxin, as compared with 90 per cent in Fraser and Halpern's series; third, 91 per cent had 1/10 unit or above, as compared with 78 per cent of Fraser and Halpern's group. There were none with very high antitoxic levels.

The recent work of Bigler and Werner [1c] on immunization with the combined alum-precipitated diphtheria and tetanus toxoid is unfortunately not strictly comparable, since in their series blood was withdrawn for serum titration at periods varying from one to twenty months after immunization. However, only 2 of their 240 children showed diphtheria

TABLE 4.—*Tetanus Antitoxic Levels of Blood*

Investigator	Preparation Used	Initial Doses and Interval Doses	Interval Between Immunization and Antitoxin Titration	Percentage of Subjects with Antitoxin Level * of: 0.01	0.01 to 0.1	0.1 to 1.0	1.0 and Over	Average Antitoxic Level
Hall [19c]	Alum-prec. tetanus toxoid	0.5 cc.; 0.5 cc. 8 wk. later	14 wk.	3.4	71.7	24.9	—	0.16
Bigler and Werner [1c]	Alum-prec. diphtheria and tetanus toxoid	1 cc.; 1 cc. 3 mo. later	3 mo.	5	15	55	25	0.54
Combined immunization (Lapin)	Combination of alum-prec. tetanus toxoid, etc.	0.5 cc.; 0.5 cc. 8 wk. later	3 mo.	0	6.8	72.8	20.4	0.50

* The antitoxic level is expressed in units (American) per cubic centimeter of blood serum. Tetanus antitoxin titrations were made on all serum samples at the following levels: 0.003, 0.01, 0.017, 0.02, 0.05, 0.1, 0.2, 0.5, 1.0, 2.0, 5.0, and 10.0 units.

antitoxic levels below 1/100 unit, and the general antitoxic average was high. Their work considered in conjunction with similar results of Jones and Moss [17] and of Volk and Bunney [18] seems to indicate definitely the superiority of alum-precipitated toxoid to the clear toxoid.

Immunity Against Tetanus.—This has been judged solely by the antitoxic level of the blood, since there is no intracutaneous test.

Of all the work done in this field,[19] only Bigler and Werner's [1c] and Hall's [19c] studies on large series are strictly comparable, since these

17. Jones and Moss.[1a, b] Jones, F. G.: Transactions of Laboratory and Epidemiology Sections of the American Public Health Association, Sixty-Seventh Annual Meeting, Kansas City, Mo., 1938.

18. Volk, V. K., and Bunney, W. E.: Diphtheria Immunization with Fluid Toxoid and Alum Toxoid, Am. J. Pub. Health **29**:197 (March) 1939.

19. (*a*) Ramon, G., and Zoeller, C.: Sur la valeur et de la durée de l'immunité conférée par l'anatoxine tétanique, dans la vaccination de l'homme contre le tétanos,

authors also gave two doses of alum-precipitated toxoid eight weeks apart and determined the antitoxic level of the blood about three months afterward.

Strenge [20] has expressed agreement with other workers that at least 0.1 unit of antitoxin per cubic centimeter must be present in the serum before a human being can be considered adequately protected against tetanus. From table 4 it can be seen that 93.2 per cent of the 44 children in this series may be considered adequately protected, as compared with 24.9 per cent in Hall's [19c] series and 80 in Bigler and Werner's [1c] series. Since the variation for individual subjects is large, no comparison of the "average" levels will be recorded. Thus far, I have not had the opportunity of making titrations after a period longer than three months following immunization. It is, of course, recognized that the antitoxic titer at three months after immunization represents a point on a falling curve and that retitrations at six and twelve months intervals (which I shall do) will no doubt show a lower antitoxic value. However, Bigler and Werner's [1c] recent work with combined alum-precipitated diphtheria and tetanus toxoids, in the 20 cases in which serum was titrated three months after immunization, shows results strikingly similar to mine. They found that a stimulating dose of 0.5 cc. of tetanus toxoid given one to twelve months after the original immunization produced an average of 3.65 units of antitoxin per cubic centimeter of serum on the seventh day and 4.3 units on the fourteenth day, with only 1 child of the 42 tested having a titer as low as 0.2 unit on the seventh day.

Compt. rend. Soc. de biol. **112**:347, 1933. (*b*) Sacquepée, E., and Jude, A.: Sur la valeur et la durée de l'immunité antitétanique après injection de rappel, chez l'homme immunisé contre le tétanos. Par l'emploi simultané du sérum et de l'anatoxine tétaniques, ibid. **125**:711, 1937. (*c*) Hall, W. W.: Tetanus Toxoid Immunization in the U. S. Navy, Ann. Int. Med. **14**:565 (Oct.) 1940. (*d*) Sneath, P. A. T., and Kerslake, E. G.: Further Observations Following Administration of Tetanus Toxoid, Canad. M. A. J. **32**:132 (Feb.) 1935. (*e*) Bergey, D. H., and Etris, S.: Tetanus Toxoid in Prophylaxis Against Tetanus, Proc. Soc. Exper. Biol. & Med. **30**:1037 (May) 1933. (*f*) Gold, H.: Active Immunization Against Tetanus by Means of Tetanus Toxoid Alum-Precipitated, Refined, J. Lab. & Clin. Med. **23**:903 (June) 1938. (*g*) Bergey, D. H.; Brown, C. P., and Estris, S.: Immunization Against Tetanus with Alum Precipitated Toxoid, Am. J. Pub. Health **29**:334 (April) 1939. (*h*) Marvell, D. M., and Parish, H. J.: Tetanus Prophylaxis and Circulating Antitoxin, Brit. M. J. **2**:891 (Dec. 28) 1940. (*i*) Gold, H.: On Value of Repeat Injection of Tetanus Toxoid (Secondary Stimulus) in Active Immunization Against Tetanus, J. Lab. & Clin. Med. **25**:506 (Feb.) 1940.

20. Strenge, H. B.: Immunization with Tetanus Toxoid: Recall Response, Yale J. Biol. & Med. **12**:487 (May) 1940.

Sneath,[21] giving 1,500 units of tetanus antitoxin prophylactically, secured antitoxin titers of 0.1 to 0.25 unit per cubic centimeter at the end of one week. A comparison of this passive immunization with tetanus antitoxin and active immunization with tetanus toxoid followed by a

TABLE 5.—*Results of Combined Immunization*

			Three Months After Completion of Immunization					
						Whooping Cough		
Serum No.	Name	Age at Start, Month	Schick Test	Diphtheria Antitoxic Level in Blood (Units per Cc.)	Tetanus Antitoxic Level in Blood (Units per Cc.)	Agglutination Test	Complement Fixation Test	Mouse Protection Test
4	L. K.	9	Negative	Not determined	1.0 +	3+	4+	+
5	F. L.	7	Negative	Not determined	0.5 +	4+	4+	+
6	P. D.	9	Negative	Not determined	0.2 +	2+	4+	Q.N.S.
7	C. A.	9	Negative	Not determined	0.2 +	4+	4+	+
8	L. F.	6	Negative	Not determined	0.5 +	4+	4+	+
9	A. F.	8	Negative	Not determined	0.2 +	4+	4+	—
10	R. F.	7	Negative	Not determined	0.2 +	2+	4+	+
11	S. B.	9	Negative	Not determined	0.2 +	3+	3+	+
12	E. A.	9	Negative	Not determined	0.5 +	4+	4+	+
13	G. L.	9	Negative	0.1+	0.2 +	4+	—	+
14	A. C.	8	Negative	0.1+	0.2 +	4+	4+	+
15	C. F.	7	Negative	Q. N. S.	1.0 +	4+	2+	+
50	E. T.	8	Negative	Q. N. S.	0.2 +	4+	4+	+
51	S. P.	9	Negative	0.1 +	0.05+	4+	4+	—
52	F. F.	8	Negative	0.002+	0.2 +	4+	4+	+
53	B. F.	8	Negative	0.01+	0.2 +	4+	3+	+
54	H. W.	7	Negative	Q. N. S.	Q. N. S.	4+	Anticomp.	Q.N.S.
55	E. T.	6	Negative	0.1 +	0.05+	4+	4+	+
56	G. G.	8	Negative	0.1 +	0.2 +	4+	4+	+
57	E. A.	7	Negative	0.1 +	0.2 +	4+	4+	+
60	L. L.	7	Negative	Q. N. S.	0.2 +	4+	4+	+
61	R. H.	8	Negative	0.1 +	0.2 +	4+	4+	—
62	C. M.	8	Negative	0.1 +	0.2 +	4+	4+	+
63	M. P.	9	Negative	0.1 +	0.2 +	4+	4+	+
64	L. F.	6	Negative	0.1 +	0.2 +	4+	4+	+
65	A. R.	8	Negative	0.1 +	0.2 +	4+	Anticomp.	+
66	J. H.	9	Negative	0.1 +	0.2 +	4+	4+	+
67	L. C.	24	Negative	0.1 +	0.05+	4+	4+	+
68	A. D.	9	Negative	0.1 +	0.2 +	4+	4+	+
69	S. K.	6	Negative	0.1 +	0.2 +	4+	4+	+
71	B. P.	7	Negative	0.1 +	0.2 +	4+	4+	+
72	S. N.	10	Negative	0.1 +	0.2 +	4+	4+	+
73	I. C.	6	Negative	0.1 +	0.2 +	4+	4+	+
74	S. L.	8	Negative	0.1 +	0.2 +	4+	4+	+
75	D. S.	8	Negative	0.1 +	0.2 +	4+	4+	+
76	M. C. A.	8	Negative	0.1 +	0.2 +	4+	4+	+
77	H. N.	24	Negative	0.1 +	1.0 +	4+	4+	+
78	P. N.	75	Negative	0.1 +	2.0 +	4+	4+	+
79	N. B.	7	Negative	0.01+	0.2 +	4+	4+	+
81	M. L.	9	Negative	0.1 +	1.0 +	4+	4+	+
82	P. B.	7	Negative	0.1 +	1.0 +	4+	2+	—
83	S. L.	9	Negative	0.1 +	1.0 +	4+	2+	+
84	J. F.	10	Negative	0.1 +	1.0 +	4+	2+	+
85	E. F.	7	Negative	0.1 +	0.2 +	4+	2+	+
86	R. W.	9	Negative	0.1 +	1.0 +	4+	4+	—

stimulating dose of tetanus toxoid on exposure to tetanus shows the superiority of tetanus toxoid immunization. From Rogers'[21a] and Bigler and Werner's[1c] work, it can now be stated definitely that even the subjects whose antitoxic levels were below 0.1 cc. three months after

21. Sneath, P. A. T.: Degree of Protection Afforded by Tetanus Toxoid, Canad. Pub. Health J. **25**:195 (April) 1934.

21a. Rogers, R. P.: Bull. New York Acad. Med. **15**:553 (Aug.) 1939.

the primary injections (6.8 per cent of my series) will have a safe level when a stimulating dose is given.[22] In addition, Ramon [2] showed that when 1,000,000 men were immunized with tetanus toxoid and soldiers exposed to tetanus infection were given a boosting dose of toxoid not a single case of tetanus occurred.[23]

Immunity Against Whooping Cough.—In lieu of the usual mass immunization studies, immunization against whooping cough has been judged, first, by the agglutination reaction against H. pertussis; second, by complement fixation against H. pertussis, and, third, by the results of mouse protection tests against H. pertussis.

The results of the rapid agglutination test have been remarkably uniform, with the blood serum of 100 per cent of the immunized children showing positive agglutination, 89.8 per cent 4 plus, 5.1 per cent 3 plus and 5.1 per cent 2 plus. Comparison of the results of combined immunization with those of the usual method of immunization against whooping cough has been possible for only a small series. In tests on the serum of 10 children who had received the customary doses of Sauer vaccine, the agglutination was 4 plus in only 2 instances, 3 plus in 1 and 2 plus in 7. A feature of the rapid agglutination test setting it apart from the usual agglutination tests is the fact that the reaction remains positive for a much longer period after immunization. With the usual agglutination test the reaction becomes negative in less than a year after immunization. On the other hand, 19 tests done by this new rapid method on children immunized by the usual Sauer vaccine from three to five years previously showed positive results in 11.

Complement fixation reactions after immunization with the usual course of vaccine were found by Weichsel, Cohen and me [8] to become negative within nine weeks after the last dose, as compared with a persistence of positive reactions for five to eight months after an attack of the disease. Daughtry-Denmark [24] secured complete (4 plus) fixation

22. It must be again emphasized that the efficacy of active immunization with tetanus toxoid depends not on the level of antitoxin values reached three, six or twelve months after the primary immunization but on the prompt production of a marked secondary rise in antitoxin—production in response to a "boosting" dose given on the subject's exposure to tetanus. The idea that administration of a "boosting" dose when a person is exposed to tetanus may ever be dispensed with, in view of the seemingly safe antitoxic levels reached in the primary immunization, is raised only to be condemned.

23. R. Simon and G. R. Patey's recent report (Le titanos de guerre à propos des quatorze cas observés au centre sanitaire français de Besançon: Action des infiltrations anesthésiques, Presse méd. **48**:935 [Nov. 20-23] 1940) of a case of tetanus that occurred in spite of immunization has not been available for study. It was mentioned to me by Dr. C. G. Grulee in a personal communication.

24. Daughtry-Denmark, L.: Studies in Whooping Cough: Diagnosis and Immunization, Am. J. Dis. Child. **52**:587 (Sept.) 1936.

in the serum of 61 per cent of subjects immunized and positive complement fixation in the serum of 92 per cent.

A comparison of these results with complement fixation following combined immunization shows: first, complete (4 plus) fixation was found in the serum of 87.2 per cent of the subjects, and 97.4 per cent

TABLE 6.—*Results of Mouse Protection Tests* *

	Immunity Test Dose of Pertussis Culture per Cc.	Dilution of Culture				
		1:10	1:100	1:1,000	1:10,000	Result
4	L. K.	DS	SS	SS	.....	+
5	F. L.	DS	D SSSS	SS	.....	+
6	P. D. S.†	.....	.....	.....	.....	Q. N. S.
7	C. A.	DD	SSSSS	SS	.....	+
8	L. F.	DD	SSSSS	SS	.....	+
9	A. F.	.....	DDDD S	.....	.....	−
10	R. F.	DD	SS	SS	.....	+
11	S. B.	DD	SSSSS	SS	.....	+
12	E. A.	D	D SSSS	S	.....	+
	Control mice	DDDDD	DDDD S	D SSSS	SSSSS	Control
13	G. L.	D	S	S	.....	+
14	A. C.	DD	SS	DS	.....	−
15	C. F.	D	S	S	.....	+
	Control mice	DD	DD	SS	SS	Control
50	E. T.	D	S	S	.....	+
51	S. P.	D	D	S	.....	−
52	F. F.	DD	DS	SS	.....	+
53	B. F.	DD	DS	SS	.....	+
54	H. T.†	.....	.....	.....	.....	Q. N. S.
55	E. T.	DD	SS	SS	.....	+
56	G. G.	DD	SS	SS	.....	+
57	E. A.	DD	SS	SS	.....	+
60	L. L.	DD	DS	SS	.....	+
61	R. H.	D	D	D	.....	−
62	C. M.	D	D	S	.....	+
63	M. P.	DD	DS	SS	.....	+
64	L. A. F.	D	S	S	.....	+
65	A. R.	D	S	S	.....	+
66	J. H.	DD	DD	SS	.....	+
67	L. C.	DD	DD	SS	.....	+
68	A. D.	DD	DD	SS	.....	+
69	S. K.	D	D	S	.....	+
70	Control mice	DD	DD	DS	DS	Control
71	B. P.	D	D	S	.....	+
72	S. H.	D	S	S	.....	+
73	I. C.	D	D	S	.....	+
74	S. L.	D	D	S	.....	+
75	D. S.	D	S	S	.....	+
76	M. G. M.	D	D	S	.....	+
77	H. N.	D	D	S	.....	+
78	P. N.	D	D	S	.....	+
79	N. B.	D	D	S	.....	+
80	Control mice	DD	DD	DS	DS	Control

* Each mouse received intraperitoneally 0.2 cc. of serum and 1 cc. of culture in various dilutions simultaneously.

† Insufficient serum.

S indicates survival of a single mouse; D, death of a single mouse. The period of observation was 14 days.

had positive complement fixation of varying degree; second, complement-fixing reactions remained positive a much longer time than after the usual immunization, since all the subjects in this series were tested three months or more after the injections were completed.

The results of intraperitoneal mouse protection tests are shown in table 6. Mice inoculated with 0.2 cc. of serum and with varying concentrations of live pertussis organisms were compared with a control

series of mice inoculated with live pertussis bacilli only. When more mice in the serum-protected group than in the control group survived the injection, the mouse protection titer is called positive. Thus serum 8 (L. F.) protected 5 of the 5 mice given a 1 : 100 dilution of the culture, while only 1 of the 5 control mice was protected. Where there was no difference in the survival rate between the serum-protected and the control mice, the result was called negative. Thus serum 9 (A. F.) protected 1 of 5 mice given a 1 : 100 dilution of the culture, and 1 was protected among the controls also. There are unaccountable variations in the virulence of the pertussis organism, and in many instances in this study not enough serum was on hand to use a large number of mice. On the whole, however, there is a striking correlation in my group between the results of the serologic tests, such as agglutination and complement fixation, and the results of the mouse protection test. About 87.5 per cent of the children receiving the combined immunization had a positive mouse protection titer. Unfortunately, there has been no work recorded in the literature in which intraperitoneal mouse protection tests were done after the usual immunization with Sauer vaccine; so a direct comparison is impossible. Mishulow and associates [25] found that the serums of 30 of 38 children taken during the course of clinical whooping cough protected from 31.3 to 100 per cent of the mice. The same workers found the serums of 5 of 8 convalescent patients definitely protective, while none of the serums of 8 normal human subjectes showed any protection. This comparison, of course, is too indirect to be of much value.

COMMENT

The combined immunization against diphtheria, tetanus and whooping cough used as routine prophylaxis for well children has certain advantages. With respect to the number of injections necessary, there has been a gradual change and improvement in the methods of immunization of well children. Originally three injections of clear diphtheria toxoid, two of tetanus toxoid and three of pertussis vaccine were used. More recently, especially since the work of Bigler and Werner,[1c] it has become possible to accomplish the same end by two injections of combined alum-precipitated diphtheria and tetanus toxoids and three of pertussis vaccine. Since reactions with pertussis vaccine are rather frequent, there may be some advantage in my combined method, in which the five monthly injections allow for a maximum dose of 20,000,000,000 pertussis organisms, instead of the usual increase to 40,000,-

25. Mishulow, L.; Klein, I. F.; Liss, M. H., and Leifer, L.: Mouse Protection Tests in Whooping Cough, J. Immunol. **37**:17 (July) 1939.

000,000 at an injection. There may also be some value in fitting these injections into the usual routine monthly visits to the pediatrician.

On the basis of the small series reported here, immunity against diphtheria results in a 100 per cent incidence of negative reactions to the Schick test. However, in a larger series of subjects, for whom combined diphtheria and tetanus toxoid was used, positive reactions were occasionally encountered. It seems probable that occasional positive Schick reactions will be found also in a more extensive series of the subjects given the combined tetanus, diphtheria and pertussis immunization. Another group of children, immunized too late for inclusion in this report, have received the alum-precipitated diphtheria toxoid in their final injection. Bigler and Werner's [1e] recent results seem to show the superiority of alum-precipitated diphtheria toxoid to the clear toxoid, and perhaps it will prove wiser in the future to use the combination of alum-precipitated diphtheria and tetanus toxoids, together with the whooping cough vaccine and whooping cough toxin, in this plan for routine prophylaxis.

In 93.2 per cent of cases the immunity against tetanus resulted in an antitoxic level of above 0.1 unit. In these and in the remaining 6.8 per cent, it seems proved that the boosting dose given on the subject's exposure to the disease can be depended on to produce a quick rise to a safe level. This removes the real stumbling block to popularization of immunization with tetanus toxoid.

The immunity against whooping cough, judged by the results both of serologic and of intraperitoneal mouse protection tests, is definitely greater than that produced by the usual individual immunization.

The duration of immunity cannot yet be predicted; serum titrations will be repeated at periods of one, two and three years, and the effect of a "boosting" dose including diphtheria, tetanus and whooping cough vaccine in one injection will be studied at those periods.

SUMMARY

Seventy-eight infants from 6 to 9 months of age were given a combined immunization with clear diphtheria toxoid, alum-precipitated tetanus toxoid, whooping cough vaccine and whooping cough toxin in five monthly injections. The immunity response was as follows:

1. Diphtheria immunization resulted in negative Schick reactions for 100 per cent of the subjects, 97 per cent having above 1/250 unit of antitoxin per cubic centimeter of blood and 91 per cent having above 1/10 unit per cubic centimeter.

2. Tetanus immunization resulted in an increase of the average antitoxic level to 0.50 unit, with 93.2 per cent of the subjects having three months after immunization an antitoxic level greater than is attained

by the usual prophylactic injection of tetanus antitoxin. Evidence has been cited to show that the 6.8 per cent who had titer below this level at the three month period following immunization have a sound "basal immunity" and on exposure will respond to a boosting dose with a safe antitoxic level.

3. Whooping cough immunization resulted in positive reactions to agglutination tests for 100 per cent of the subjects, complement fixation of 4 plus for 87.2 per cent and positive for 97.4 per cent, and a positive mouse protection titer for 87.5 per cent.

NOTE.—In some unreported work by Miller,[26] after the use of pertussis vaccine and tetanus toxoid, the tetanus antitoxic titers were not so high as those obtained with tetanus-diphtheria toxoid. Kendrick,[27] using pertussis vaccine and diphtheria toxoid, secured diphtheria and pertussis antitoxic titers at least as high as when the immunizing substances were given separately.

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26. Miller, J. J., cited by Grulee, C. G.: Personal communication to the author.

27. Kendrick, P. L.: Simultaneous Alum-Precipitated Combined Diphtheria Toxoid and Pertussis Vaccine, J. Bact. **42**:294 (Aug.) 1941.

OBESITY IN CHILDHOOD

PSYCHOLOGIC STUDIES

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Several hundred obese children have been referred to us as having Fröhlich's syndrome, or dystrophia adiposogenitalis. These patients were presumed to have pituitary disease or a combination of pituitary with thyroid involvement. Approximately 80 of this number [1] have been studied thoroughly from the point of view of physical development (sexual and mensurational) (fundi and visual fields), and complete laboratory studies were made, including roentgenographic examination of the head (sella turcica), wrist and knee, and basal metabolism, blood cholesterol and sugar tolerance tests. In addition, we have used a roentgenographic cephalometric appraisal [2] to study the problem further. Analysis of the craniofacial system by this method showed that in general the skeletal development in an unselected group of some 20 obese boys and girls was normal and even in advance of that in normal controls. We have also made cephalometric studies of thyroid-deficient [3] and dwarfish [4] (pituitary) children and so have data on both hypothyroidism and hypopituitarism for comparison.

Based on a thesis presented to the Department of Psychology, University of Illinois, June 1941.

From the department of Pediatrics (Endocrine Clinic) and the Institute for Juvenile Research, University of Illinois College of Medicine and the Research and Educational Hospital.

1. Bronstein, I. P.; Halpern, L. J., and Brown, A. W.: Physical Studies in Obesity of Childhood, unpublished data.

2. Bronstein, I. P., and Massler, M.: Cephalometric Appraisal of Obesity in Childhood, unpublished data.

3. Engel, M. B.; Bronstein, I. P.; Brodie, A. G., and Wesoke, P.: A Roentgenographic Cephalometric Appraisal of Untreated and Treated Hypothyroidism, Am. J. Dis. Child. **61**:1193 (June) 1941.

4. Massler, M., and Bronstein, I. P.: Cephalometric Appraisal in Dwarfism, unpublished data.

From our other studies of adipose children, we have come to the conclusion that neither pituitary nor thyroid disease need be postulated. We do not deny, however, the possibility of a temporary aberration in the endocrine system or in the hypothalamus, which may spontaneously correct itself at puberty except in those children who are mentally retarded. In the treatment of obese children, endocrine therapy did not cause any alteration in the redistribution of fat. Chorionic gonadotropin, while influencing the descent of undescended testes and genital enlargement, did not affect the adiposity, nor did any other pituitary preparation administered orally or parenterally. Thyroid therapy also proved to be of little value.

Since with so many of the children overeating was influenced by environmental and various psychologic factors, one purpose of this study was to determine whether the milieu of these children was of a characteristic type which predisposed them to such a habit. Other purposes were to determine objectively the masculinity or femininity of these obese children, to study the educational level of the group through the use of achievement tests and to obtain some objective measure of the personality of the children.

There are few studies of this nature reported in the literature on the obese child. Recently Levy [5] and Bruch [6] have reported excellent studies on children with the so-called Fröhlich syndrome. Levy found that his group of 33 obese boys was of high average intelligence. The group was predominantly submissive in behavior and the submission was considered as due to a constitutional factor. This conclusion was based on impressions gained from various interviews.

Bruch found that the majority of the children she studied were of average or superior intelligence and that as a group they exhibited few interests or talents. They were socially immature, disliked accepting responsibilities and lacked most of the characteristics of independent behavior. Many of them expressed fear of danger, failed to enter into games and preferred sedentary occupations. Ordinal position in the family was considered as playing an important part in their obesity.

METHOD OF STUDY

The material for this paper was gathered for a battery of five tests, from the history given by the parent or guardian who accompanied the child to the clinic and from our records.

5. Levy, D. M.: Aggressive-Submissive Behavior and the Fröhlich Syndrome, Arch. Neurol. & Psychiat. **36**:991 (Nov.) 1936.

6. Bruch, H.: (*a*) Energy Expenditure in Obese Children, Am. J. Dis. Child. **60**:1082 (Nov.) 1940; (*b*) Physiologic and Psychologic Aspects of the Food Intake of Obese Children, ibid. **59**:741 (April) 1940; (*c*) Physical Growth and Development of Obese Children, ibid. **58**:457 (Sept.) 1939.

The number of children studied was 35, 24 boys and 11 girls. No method of selection was employed other than that of writing letters of appointment to the parents of those patients in the Fröhlich syndrome file.

The average time spent on each patient, solely in terms of test administration, was approximately three hours. A number of children, because of mental as well as chronologic immaturity, were given only two or three tests and more emphasis was placed on the interview with the parent.

The tests used were the revised Stanford-Binet intelligence scale, form L, the new Stanford reading and arithmetic achievement tests, the Pinter "aspects of personality" and the Terman-Miles attitude-interest analysis scale, form B. The Terman-Miles test is a disguised masculinity-femininity test and hereafter will be referred to as the masculinity-femininity (M-F) test. These tests were selected because of their general applicability to the age range of the children that were tested. Although the authors realized the shortcomings of personality tests in general and also of the masculinity-femininity test, nevertheless the former were used to secure an objective determination of personality deviation and the latter to check on the frequently held notion concerning the femininity of the boys. With the exception of the revised Stanford-Binet, none of the tests previously mentioned has been used in similar studies, as far as can be determined.

The subjects of this study were arbitrarily divided into three groups. Group 1 consisted of the children whose intelligence quotients were above 110; group 2 of those with quotients from 90 to 109 inclusive, and group 3 of those with quotients below 90. The essential data for these groups are given in tables 1, 2, and 3. A description of two children, a boy and a girl, representative of each group follows:

GROUP 1: INTELLIGENCE QUOTIENT ABOVE 110

CASE 12 (fig. 1).—H. S., was a boy, aged 10 years, 10 months. The mother showed extreme anxiety over the test situation. She stood with her ear pressed against the door for about an hour and a half, while a single test was being administered. At intervals she opened the door slightly and smiled at the boy.

She reported that the patient was sensitive about his weight and responded to teasing by retreating into the house. He read a great deal, listened to the radio much of the time and attended movies twice a week. He enjoyed school work and had good grades. Most of his friends were older, and he tended to be the follower in the crowd. He was well behaved and got along well with his three sisters. He had many hobbies, but would rather sit and watch games than participate in them. He liked to be busy all the time, but tired easily and in general was not persevering. The patient was not allowed to do anything or to go anywhere alone and had to keep his mother informed of his whereabouts at all times.

He was thin until he was 4 years of age, when he had a tonsillectomy and began to gain weight. In spite of the fact that the parent brought him for reducing purposes, he continued to gain weight and no curb was put on his appetite because, as his mother said, "He'll get weak if I keep him on a diet." She also said that originally she was worried about him because a pharmacist told her that the boy's glands were at fault, and no amount of reassurance could convince her to the contrary. This is an example of how an injudicious statement inadvertently given may interfere with effective therapy.

TABLE 1.—*Intelligence Quotients Above 110*

Number	Sex	Nationality	Age at Entrance Yr.	Age at Entrance Mo.	Height at Entrance, Inches	Weight at Entrance, Pounds	Per Cent Overweight	Intelligence Quotient	Masculine-Feminine	Reading	Arithmetic	Ascendancy-Submission (Percentiles)	Extroversion-Introversion (Percentiles)	Emotional Stability (Percentiles)
1	M	Mixed	12	5	61	155	65	147	M	Advanced	Retarded	37	5	36
2	F	Jewish	12	4	59	120	33	119	F	Advanced	Advanced	94	94	49
3	M	Mixed	9	6	55	115	63	116	M	Advanced	Retarded	5	9	53
4	M	Mixed	14	3	70	253	84	115	M	Advanced	Retarded	100	93	1
5	M	Jewish	8	3	57	117	56	125	..	Up to grade	Up to grade	42	58	36
6	M	Jewish	13	4	65	153	28	136	M	Advanced				
7	M	Mixed	10	7	66	170	32	116	M	Advanced	Retarded	98	83	6
8	F	Jewish	12	0	57	125	45	115	F	Retarded	Retarded	14	9	53
9	M	Mixed	12	8	64	194	74	124	M	Advanced	Retarded	77	32	13
10	M	German	10	1	56	105	36	126	M	Advanced	Up to grade	37	6	75
11	F	Mixed	12	3	61	165	57	119	M	Advanced	Up to grade	48	3	23
12	M	Jewish	8	10	54	114	58	130	M	Advanced	Up to grade	32	76	76
13	M	Mixed	8	3	56	89	18	137	F	Up to grade	Retarded	78	94	36
14	M	Italian	11	4	58	142	69	111	M	Retarded	Retarded	55	32	10
15	M	Mixed	11	6	51	76	24	115	M	Retarded	Advanced	37	79	92
16	M	Jewish	12	6	63	180	68	120	M	Up to grade	Advanced	63	79	92
17	M	Jewish	12	6	61	168	64	123	F	Up to grade	Retarded	19	79	36
Means.....			11	4	59.6	152	52	123						

There were four children in the family; three were girls, ranging in age from 18 to 25, and the fourth was the patient. The age interval between the youngest girl and the patient was eight years. None of the girls or the parents was obese.

On the basis of chronologic age he was one year advanced in school, but on the basis of his mental age he was two and one-half years retarded. His reading achievement was at his mental age level, and his arithmetic was in agreement with his actual grade placement. His masculinity score was about average. Personality test scores indicated a tendency toward submissiveness, extroversion and emotional stability.

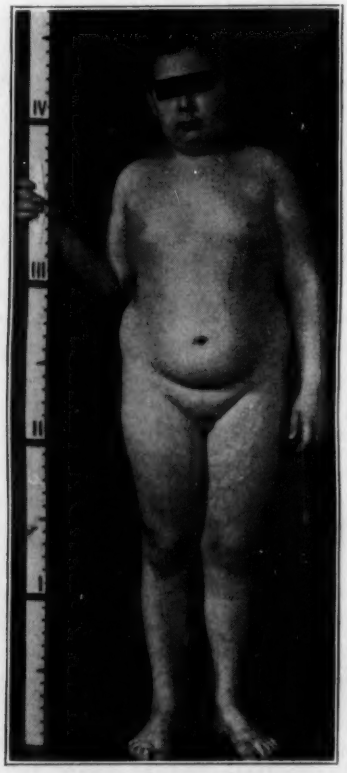

Fig. 1.—H. S., aged 10 years, 10 months.

CASE 11.—O. K., aged 13 years, 9 months, was a large obese girl, who left her mother only after much persuasion. She was sensitive about her overweight and resented any comments about it. She did not care to mingle with other children, read a great deal, listened to the radio much of the time and was "crazy" about the movies. She was an honor student at school. She had always been heavy, but her weight had become noticeable in the last five years. She had the "appetite of ten people."

The patient was shy with strangers but soon became talkative and overflippant with people whom she knew casually. She was easily angered but calmed down

quickly. She was affectionate, obedient, strong minded, active and "afraid of nothing." She was not allowed to go anywhere alone and did not know how to use the street car.

There were two children in the family, both girls. The patient was the younger of the two, and the mother reported that the girls fought like "cats and dogs." The father had died about twelve years previously, and the mother had worked ever since. Recently she had been employed at night and had not seen much of her daughters.

The father's family were all tall and heavy, while the mother's family were all small and light.

The patient was one-half year retarded in school on the basis of her chronologic age. Her reading achievement was on a par with her mental age, and her arithmetic was at her actual grade level. Her masculinity-femininity test score indicated a strong tendency in the direction of masculinity. Personality test scores indicated ascendance-submission about average, but she was extremely introverted and showed a slight degree of emotional instabiliy.

Comment on Group 1.—This group consisted of 17 children, 14 boys and 3 girls. The mean intelligence quotient was 123, with a range from 111 to 147. These children were 52 per cent overweight. The masculinity-femininity test scores were average for all except 3, 2 boys with a deviation in the direction of femininity and a girl who deviated toward masculinity. Personality test scores indicated that 4 patients were ascendant, 3 submissive, 7 extroverted, 5 introverted and 3 emotionally unstable. Four others had a tendency toward submissiveness, and 7 had a tendency toward emotional instability.

Eight of the group were sensitive about their weight and 5 were not, 1 girl in each category. The majority of the children spent a great deal of their time in reading, listening to the radio and attending movies. Five of the group had many friends about the same age; 5 had a few who were older, and 2 had an average number of the same age. In 4 cases either the parents of the child were separated, or the father was dead and the mother was the sole support of the child, or children, and so saw little of them. In this group there were a few one child families, 7 two child, 4 three child and 1 four child. Of the total of 16 children reported on, 12 were either the only or the last child.

GROUP 2: INTELLIGENCE QUOTIENTS BETWEEN 90 AND 109

CASE 9 (fig. 2).—J. K., a boy aged 11 years, 5 months, was an adopted child but, according to his foster-mother, was not aware of the fact. There is no information about his real parents. He was an only child and had been a constant source of trouble to his foster-parents. Recently he had consistently refused to go to school, because he claimed that the teacher did not give him enough attention. He was sensitive about his obesity and got angry easily, at which time he wanted to break things. He smashed the radio because it was not playing loud enough to suit him. Despite his easily aroused temper, he did not care to fight. He read little aside from the comics, listened to the radio much of the time

TABLE 2.—*Data on Group 2: Intelligence Quotients Between 90 and 109*

Number	Sex	Nationality	Age at Entrance Yr.	Age at Entrance Mo.	Height at Entrance, Inches	Weight at Entrance, Pounds	Per Cent Overweight	Intelligence Quotient	Masculine-Feminine	Reading	Arithmetic	Ascendancy-Submission (Percentiles)	Extroversion-Introversion (Percentiles)	Emotional Stability (Percentiles)
1	M	Jewish	11	4	58	110	30	97	M	.....	.....	37	55	100
2	M	Mixed	13	1	60	147	58	98	M	Retarded	Retarded	88	55	42
3	M	Colored	4	11	47	76	55	108						
4	F	Mixed	8	0	52	95	67	109	M	Advanced	Advanced	27	72	58
5	M	Mixed	13	3	59	107	20	92	..	Retarded	Advanced	71	93	100
6	F	Jewish	14	1	59	137	42	90	F	Retarded				
7	M	German	10	10	56	113	65	101	..	Advanced	Retarded	15	11	64
8	F	Swedish ?	8	6	56	135	77	103	..	Up to grade	Retarded	43	35	78
9	M	Mixed	12	9	65	201	71	92	..	Retarded	Retarded	72	35	31
Means.....			10	6	57	124	54	98						

and went to movies about three times a week. He had threatened to run away from home on several occasions. He made friends easily and had a number his own age. He had a large appetite, and his favorite food was spaghetti.

He was about two years retarded in school for his reading and arithmetic achievements were at the third grade level, which was three years below his actual grade and five years below the standard for his chronologic age. He was fairly ascendant and had a tendency toward introversion and emotional instability.

Fig. 2.—J. K., aged 13 years, 5 months.

CASE 4 (fig. 3).—B. J. H., a girl aged 12 years, 10 months, was the second of three siblings. She did not get along well with the others. She was disturbed when teased about her obesity. She had an average number of friends, mostly of her own age, but she would have liked to have more children pay attention to her. She liked movies, listened to the radio much of the time and recently had been reading more than usual.

She was properly placed in school for her chronologic age, but her achievements were two years superior to her actual grade. Her femininity score deviated from the average of her group. She tended toward submissiveness and extroversion and was emotionally stable.

Comment on Group 2.—This group consisted of 9 children, 6 boys and 3 girls. The mean intelligence quotient was 98, with a range from 90 to 109. Only 4 masculinity-femininity tests were given to this group because of the low mental or chronologic age of the children. Only 1 girl showed any tendency to deviate from the mean of the group for her grade level; this was in the direction of masculinity. Personality test scores of 7 of the 9 children indicated that 3 were ascendant, 1 was

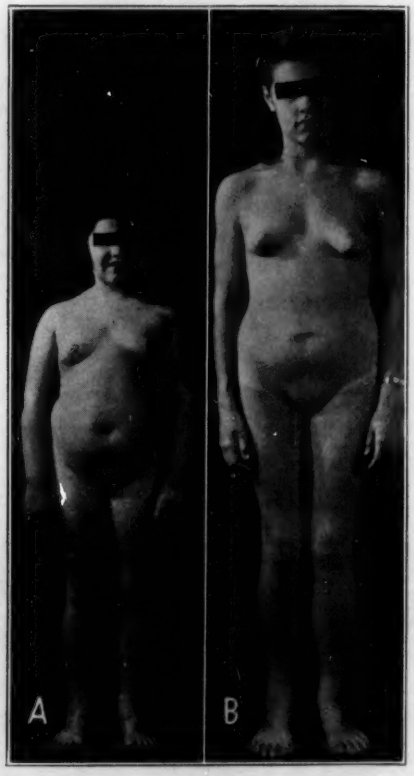

Fig. 3.—B. J. H. at entrance (*A*), at the age of 8 years, and at the age of 11 years (*B*). Spontaneous correction after three years.

submissive, 2 had a tendency toward submissiveness, 1 was extroverted, none was introverted and 6 were emotionally unstable. The average per cent of overweight for this group at the time of entrance of the patients to the clinic was 54.

From the report of the parents, 4 children were sensitive about their weight and 3 were not. The majority of the children spent much of their time in reading, listening to the radio and going to the movies. Three were reported to have many friends, 1 to have an average number and 2 to have few or none. Only 1 had an employed mother. There

were 2 one child families, 4 two child and 1 three child. Five of the 7 patients reported on were either the only or the last child. Five were reported to have a good or big appetite and 1 an average.

GROUP 3: INTELLIGENCE QUOTIENTS BELOW 90

CASE 1 (fig. 4).—B. V., a girl aged 11 years, 9 months, had been out of school a year, because of slowness and inability to get along with other children. Since remaining out of school she disliked leaving the house or meeting people. She

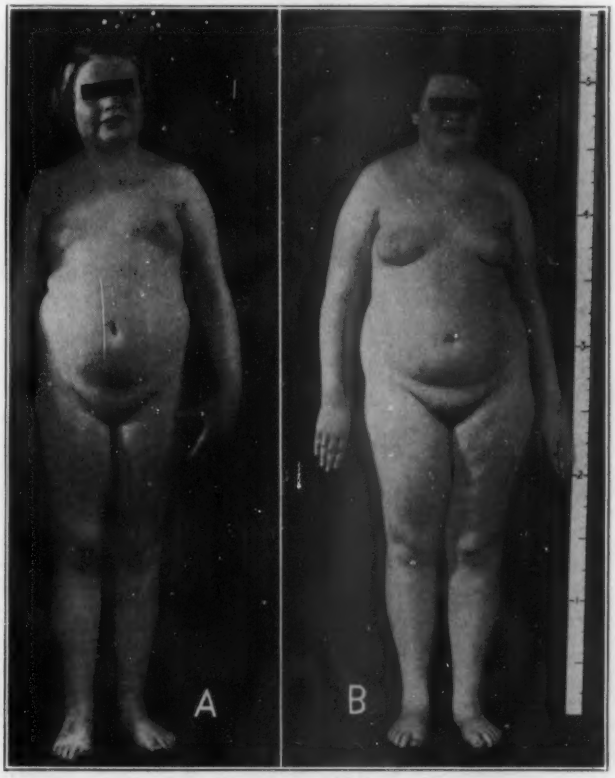

Fig. 4.—B. V. at entrance (*A*), at the age of 7 years, and at 11 years 9 months (*B*). Condition unchanged, in contrast with case 4 (fig. 3).

"loves" to be with children, and occasionally the younger ones in the neighborhood played with her. She liked to read, did not care for the movies and listened to the radio "all the time." She was "not afraid of anything"; however, she would never go to school alone. She had a large appetite and drank a great deal of water. Her older brother was normal. The father's family was tall and heavy; the mother was also inclined to be overweight.

CASE 5.—G. S., a boy aged 13 years, 8 months, was an only child. He had always been heavy and had a voracious appetite. He was imaginative and during

TABLE 3.—*Data on Group 3: Intelligence Quotients Below 90*

Number	Sex	Nationality	Age at Entrance Yr.	Age at Entrance Mo.	Height at Entrance, Inches	Weight at Entrance, Pounds	Per Cent Overweight	Intelligence Quotient	Masculine-Feminine	Reading	Arithmetic	Ascendancy-Submission (Percentiles)	Extroversion-Introversion (Percentiles)	Emotional Stability (Percentiles)
1	F	Mixed	6	2	54	86	53	52						
2	M	Jewish	7	7	55	118	63	76	..	Up to grade	Up to grade	42	3	31
3	M	Mixed	11	0	56	110	42	59	..	Advanced	Up to grade	59	8	51
4	F	Jewish	7	1	49	79	45	63						
5	M	Jewish	12	5	54	102	43	53	..	Retarded	Retarded			
6	F	Italian	10	10	59	142	57	57	..	.....	.....	19	81	58
7	F	Mixed	9	3	55	113	52	82	..	Retarded	Retarded			
8	F	P ?	8	9	54	145	107	39						
9	M	Colored	11	9	59	164	84	78	..	Advanced	Retarded	72	94	8
Means.....			8	5	55	118	57	63						

the tests was demonstrative and affectionate; he insisted on shaking hands every few minutes and talked incessantly. The mother reported that he read little, liked the movies a great deal and when at home had the radio on "all of the time." When the other children teased him about his weight, he merely walked away. He liked to meet people but had few friends, most of them younger than himself. He was slow in everything and did not participate much in activities, because he was always afraid of being hurt. He liked to play by himself, was fidgety and talked in his sleep occasionally. The maternal side of the family was obese; both families were about average height. The mother said that there was no mental retardation in either her or her husband's family. She felt that the child had become more troublesome recently, but said that this annoyance might be partly due to her being nervous and to the fact that the boy "takes after me anyway."

He was in grade 5A, which was three years below the grade level for his chronologic age. He was slightly advanced for his mental age, and his achievements were at the second grade level.

Comment on Group 3.—This group consisted of 9 children, 4 boys and 5 girls. The mean intelligence quotient was about 63, with a range from 39 to 82. This group was 57 per cent overweight. Because of the mental immaturity of the group, only four personality tests and no masculinity-femininity tests were given. Personality tests indicated that 2 children were introverted, 1 submissive, 2 extroverted, 1 ascendant and 1 unstable. Even in the cases in which the tests were given the results were doubtful, because of the mental level of the group.

Three children were sensitive about their weight. Five were much interested in the radio; 3 read a great deal, though their reading material was at the comic book level, and 4 enjoyed movies greatly. Two were reported to have many friends and 4 to have few, if any. Two were from one child families, and 1 from a four and 1 from a five child family. Six of the 9 were either the only child or the last child.

SUMMARY OF AND COMMENT ON RESULTS

For the total group the range of intelligence quotients was from 39 to 147, a spread of 108 points. The median intelligence quotient for the group was 109. There was a definite tendency toward superiority in intelligence as shown by the tests. On the basis of the usual classification, about 48 per cent of the children were superior, 25 per cent were average and another 25 per cent were below. Levy's group showed the same trend. He found slightly more than 48 per cent in the superior class, but about 35 per cent in the average, as contrasted with the 25 per cent of this study. The chief difference between the two groups insofar as intelligence is concerned was in the retarded class, in which Levy had only 11 per cent of his total, whereas we had 25 per cent. These numbers, however, are too small for definite conclusions.

In reading and arithmetic the superior children were advanced, the average ones up to grade and the dull ones retarded for their chronologic age.

Masculinity-femininity scores for the group generally were about average as far as can be determined from the Terman test. Four children showed a deviation from the norm; 3 of them were in the superior class and 1 in the average. Two boys of group 1 deviated in the direction of femininity, and 2 girls, 1 superior and 1 average, deviated in the direction of masculinity. No scores were obtained for the retarded group, because of the mental immaturity of the children.

Personality tests of the group for ascendancy-submission, extroversion-introversion and emotional stability indicated that 8 children were ascendant and 5 submissive and 2 had a tendency toward submissiveness. Ten were extroverted, 4 had a tendency toward extroversion and 7 were introverted. Six were emotionally stable, 4 showed emotional instability and 7 had a tendency in this direction.

Fifteen children of the total group were reported by the parents as being sensitive about their weight and 8 as not being sensitive; no data were secured for 12. The majority were highly interested in reading, listening to the radio and going to the movies. Ten had many friends, 3 an average number and 11 a few. The mothers of 5 of the children worked and saw little of them.

The size of the families ranged from one to five members; about half the families had only two children and a fourth had only one child. Of the 18 subjects from two child families, 11 were second children and 7 were first. Of the total group, 14 subjects (40 per cent) were last-born children.

The total group of children was about 54 per cent overweight at the time of entrance to the clinic. The boys were 53 per cent overweight and the girls 60 per cent. The children of group 1 were 52 per cent overweight, group 2 54 per cent and group 3 57 per cent. Eighteen children of the total group were reported as having a "very good," "big" or "voracious" appetite.

Of the entire group of 35 subjects, 9 reported obesity on the maternal side of the family and 4 on the paternal side. Of all the children, only 4 reported the presence of obesity in relatives. It must be remembered, however, that the report varied in terms of what the parents considered obese.

Twelve children (34 per cent) of the group were Jewish, 2 German, 2 Italian, 1 Swedish and 1 Polish; the nationalities of the remainder were mixed or undetermined.

CONCLUSIONS

From comprehensive physical studies of these 35 children, no ascertainable endocrinologic evidence was found as a basis for their obesity.

The mean intelligence of this group was above the mean of the population as a whole. There seemed to be a tendency for the children to fall into two classes, superior and retarded; almost 50 per cent were above average and 25 per cent below.

As far as can be determined from achievement tests, these children showed little or no difference from children of similar capacity.

Of 24 boys, only 2 showed a tendency toward femininity. Thus, so far as could be determined by the Terman-Miles test, this group showed no greater tendency toward femininity than might be expected of any comparable group. This is contrary to the view held by many.

The "aspects of personality" test indicated that the subjects were no different from other children as far as ascendancy-submission was concerned, but that they had a tendency toward extroversion and instability.

There was a definite tendency for the children to be sensitive about their obesity.

A large majority of the children were reported to be interested in sedentary play activities, such as going to the movies, listening to the radio and reading.

There is no known history of obesity in the majority of the parents or siblings of these children.

Fifty per cent of the patients came from families with two children, 25 per cent from families with one child and another 25 per cent from families with more than two children.

Finally, it may be emphasized that in the absence of any physical defects the adiposity of these children was probably contributed to by their sedentary habits, their abnormal appetites, parental attitudes and other environmental factors.

ESSENTIAL FRUCTOSURIA

ITS PATHOPHYSIOLOGY

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In 1876 Zumier [1] and Czapek [2] each reported the occurrence of fructose in the urine of a nondiabetic patient. Though it is clear that in both cases fructose was present in the urine, there are insufficient data in the reports of these authors to warrant the conclusion that they were dealing with instances of the syndrome of essential fructosuria. Since 1876 there have appeared some thirty-seven reports describing 55 cases of essential fructosuria (table 1). Of these, sixteen do not give sufficient data to confirm the diagnosis.

Though several of the more recent reports contain some experimental results, there has as yet been none which substantiates an explanation of the mechanism of essential fructosuria. This paper reports the cases of 2 brothers with essential fructosuria, together with some experimental results leading toward a possible explanation of the mechanism of this condition.

REPORT OF CASES

CASE 1.—A. G., a 7 year old Jewish boy, was admitted to the hospital with complaints of fever (temperature up to 102 F.), fatigue, sore throat and generalized aches and pains, all of one to two weeks' duration. A paternal second cousin and her 2 children are at present being treated at another institution for diabetes mellitus. Through the cooperation of Dr. A. E. Fischer, these relatives were examined and found not to have fructosuria.

On admission the child was subacutely ill; the pharynx was intensely injected. The heart was not enlarged on percussion; the rate was rapid (132 per minute); a gallop rhythm was present; the tones were poor, and a questionable murmur was heard at the apex. A reducing substance was found in the urine, but no acetone was present. After tests had given one atypical dextrose tolerance curve followed by a normal one, the reducing substance in the urine was shown to be fructose.

From the Department of Pediatrics, Dr. Benjamin Kramer, Director, and the Pediatrics Research Laboratories, Jewish Hospital of Brooklyn.

1. Zumier: Levulose im Harn eines Diabetikers, Deutsche med. Wchnschr. **2**:329, 1876.

2. Czapek, F.: Eine seltene Form von Diabetes mellitus, Prag. med. Wchnschr. **1**:265, 1876.

During the patient's stay in the hospital the heart quickly became enlarged, and there developed a blowing apical systolic murmur which was transmitted to the axilla. The quality of the heart tones became poorer. Ten days after admission the patient's condition was typical of cardiac decompensation. He was treated with oxygen, sedation and diuretics. For about four weeks the patient had decompensation and then slowly began to improve. After another two months he was in excellent condition and was discharged to a convalescent home, the diagnosis being acute rheumatic fever, rheumatic pericarditis, cardiac decompensation and essential fructosuria.

The experimental work on this boy was done during the last months of his stay in the hospital, when he had almost recovered, and was continued in the months subsequent to his return from the convalescent home.

CASE 2.—During the investigation of the family of the patient in case 1 it was discovered that a 9 year old brother, N. G., also had fructose in the urine. The past history of this patient and the physical examination revealed no other abnormality.

EXPERIMENTAL OBSERVATIONS

To establish the diagnosis of essential fructosuria certain criteria have been formulated.[3] In brief, these are: 1. A reducing substance must be present in the urine when the patient is on a regular diet and absent when the patient is given a fructose-free diet. 2. The urine when acid must show a positive Seliwanoff reaction. 3. The sugar in the urine must be levorotatory. 4. The sugar must be fermented by yeast, and after such fermentation the urine must show no rotation, a negative Benedict reaction and a negative Seliwanoff reaction. 5. The values for sugar content obtained by quantitative reduction in a specimen of urine by optical rotation and by yeast fermentation must agree. 6. A methylphenyl fructosazone should be obtained from the urine. 7. The dextrose tolerance curve must be normal.

All of the experiments for which results are reported here were performed after the patients had been on a fructose-free diet for at least forty-eight hours. Table 2 gives the evidence for considering the condition in our 2 cases essential fructosuria. Table 3 presents the results of dextrose and fructose tolerance tests.

In the various reports that have been published on this subject, there has been some speculation about which organ is responsible for the faulty metabolism of the fructose in cases of essential fructosuria. The liver and/or the kidney have been implicated as the responsible organs. In none of the publications is any evidence presented for such conclusions.

Lasker[4] has investigated the families of a number of patients with essential fructosuria and has come to the conclusion that this error in metabolism is inherited as a mendelian recessive. She has also tabulated

3. Silver, S., and Reiner, M.: Essential Fructosuria: Report of Three Cases with Metabolic Studies, Arch. Int. Med. **54**:412 (Sept.) 1934.

4. Lasker, M.: Fructosuria, Human Biol. **13**:51 (Feb.) 1941.

TABLE 1.—*Data for Cases of Essential Fructosuria in the Literature*

Author	Patient	Urine						Comment
		Reducing Substance	Levo-rotation	Seliwanoff Reaction	Yeast Fermentation	Methylphenyl Fructosazone	Reducing Substance with Sugar-Free Diet	
*Zumier [1] (1876)	29 year old Jewish man	Present	Present	..	..	..	Absent	
*Czapek [2] (1876)	29 year old Dutchman	2.3%	2.2 to 2.5%	..	..	..	..	
†Seegen, J.: Centralbl. f. d. Med. Wissensch. **22**: 753, 1884	46 year old woman	Present	Present	Positive	Positive	..	..	
*May, R.: Deutsches Arch. f. klin. Med. **57**: 279, 1896	16 year old girl	Present	0.4%	Positive	Positive	..	Absent	
Rosin, H., and Labaud, L.: Ztschr. f. klin. Med. **47**: 182, 1902	51 year old woman	0.4 to 0.9%	Present	Positive	..	Formed	Absent	Fructosemia demonstrated
Schlesinger, W.: Arch. f. exper. Path. u. Pharmakol. **50**: 273, 1903	15 year old girl	12.5% of ingested fructose excreted; after administration of 100 Gm. of sucrose 22% found in urine	Present	Positive	..	..	..	
Schwarz, L.: Deutsches Arch. f. klin. Med. **76**: 231, 1903	62 year old woman	Present	Present	Positive	Positive	..	..	
Brodersen, C. P.: Zur Kenntnis der chronische Tabaksvergiftung und der Lävulosuria, Inaug. Dissert.. Kiel, Schmidt & Klaunig, 1903; cited by Lasker [4]	36 year old German woman	Present	Present	Positive	..	..	..	Patient had chronic tobacco poisoning; autopsy revealed atrophy of liver, which author explained on basis of malnutrition
Lépine, R., and Boulud: Rev. de méd., Paris **24**: 185, 1904	32 year old woman	24 Gm.	23.5 Gm.	Positive	..	Formed	..	
Rosin, H., in Beiträge zur wissenschaftliche medicin und Chemie Festschrift Ernst Salkowski, Berlin, 1904, p. 105	51 year old woman	1.4%	1.2%	Positive	..	Formed	Absent	Fructose isolated from blood
‡Newbauer, O.: München. med. Wchnschr. **52**: 1525, 1905	30 year old man	16% of ingested fructose excreted	Present	Positive	Positive	Formed	Absent	Substance Administered / Urinary Excretion, Per Cent: Dextrose, 50 Gm. ..... 0; Galactose, 45.2 Gm. ..... 4.6; Fructose, 50 Gm. ..... 9.2; Sucrose, 50 Gm. 4.7

Jolles, A.: Wien. med. Presse **47**: 2321, 1905	(1) No details	0.24%	Present	Positive	Positive	..	..	
	(2) No details	0.16%	Present	Positive	Positive	..	..	
von Moraczewski, W.: Ztschr. f. klin. Med. **64**: 503, 1907	(1) Young female	2.5%	Present	..	..	..	Absent	
	(2) 18 year old girl	2.7%	Present	..	..	Formed	..	
Adler, O.: Arch. f. d. ges. Physiol. **139**: 93, 1911	(1) 70 year old woman	Present	0.2 to 0.7%	Positive	Positive	..	..	Calcium levulosate isolated from urine
	(2) 24 year old man	Present	0.3%	Positive	0.15 Gm. per 100 cc.	..	..	
Strouse, S., and Friedman, J. C.: Arch. Int. Med. **9**: 99 (Jan.) 1912	16 year old Jewish boy	10% of ingested fructose excreted	Present	..	Positive	..	Absent	
Barrenscheen [13] (1922)	22 year old Jewish man	9.07 to 14.15% of ingested fructose excreted	Present	Positive	Positive	Formed	Absent	Results of fructose tolerance test (50 Gm. given by mouth): Sugar — Minutes After Fructose: 0 (Urine, Gm. per 100 Cc.: 0; Blood, Mg. per 100 Cc.: 118); 15 (1.03; 179); 45 (1.93; 208); 75 (0.84; 176); 105 (0.73; 154); 135 (trace; 138); 165 (trace; 126); 195 (trace; 120). 64% of phenolsulfonphthalein excreted in 3 hours; after administration of 20 Gm. of galactose no reducing substance found in urine
Steinberg, S., and Elberg, W.: Klin. Wchnschr. **4**: 2399, 1925	(1) 21 year old woman	Present	Present	Positive	..	..	Absent	Normal dextrose tolerance curve
	(2) 30 year old sister of patient	Present	Present	Positive	..	..	Absent	Normal dextrose tolerance curve
	(3) 34 year old brother of patient	Present	Present	Positive	..	..	Absent	Normal dextrose tolerance curve

TABLE 1.—*Data for Cases of Essential Fructosuria in the Literature—Continued*

Author	Patient	Urine: Reducing Substance	Urine: Levorotation	Urine: Seliwanoff Reaction	Urine: Yeast Fermentation	Urine: Methylphenyl Fructosazone	Urine: Reducing Substance with Sugar-Free Diet	Comment
Snapper, I.; Grünbaum, A., and van Creveld, S.: Arch. f. Verdauungskr. 38:1, 1926	18 year old girl	0.5%	Present	..	Positive	..	..	Results of oral tolerance tests:
Heeres and Vos [11] (1929).....	23 year old woman	13.58 to 20.8% of ingested fructose excreted	Present	Positive	Positive	..	..	Dextrose tolerance curve normal. Results of fructose tolerance test (50 Gm. given by mouth):

Minutes After Ingestion	Sugar: Urine, Gm. per 100 Cc.	Sugar: Blood, Mg. per 100 Cc.
Dextrose, 50 Gm.		
0	0.22	90
30	0.25	144
60	0.25	160
90	0.10	134
125	0.07	92
Sucrose, 50 Gm.		
0	0.16	...
55	0.94	133
175	0.49	...
Fructose, 45 Gm.		
0	....	78
40	0.5	90
60	2.7	110
80	4.01	100

Minutes After Ingestion	Sugar: Blood, Mg. per 100 Cc.	Sugar: Urine, Gm. per 100 Cc.
0	94	0
15	107	....
30	116	0.30
60	144	1.24
90	123	1.51
120	110	1.81
150	91	0.62
180	96	0.42
210	95	0.27

Respiratory quotient:

	Before Fructose	After Fructose
Normal control....	0.71	0.95
Patient.....	0.72	0.77

Anschel, N.: Klin. Wehnschr. **9**: 1400, 1930	27 year old woman	13% of ingested fructose excreted	Present	Positive	Positive	..	Absent	Dextrose tolerance curve normal. Results of fructose tolerance test (100 Gm. given by mouth):

Minutes After Ingestion	Urine, Gm. per 100 Cc.	Sugar in Blood, Mg. per 100 Cc.	
		Total Reducing Substance	Fructose
0	0.27	90	0
60	0.198	93	16
120	4.96	105	56
180	5.93	90	40

Fischer, A.: Jahrb. f. Kinderh. **131**: 341, 1931	2½ year old girl	10% of ingested fructose excreted	Present	Positive	Positive	..	Absent	Dextrose tolerance curve normal. Results of fructose tolerance test (42 Gm. given by mouth):

Minutes After Ingestion	Sugar in Blood, Mg. per 100 Cc.	
	Total Reducing Substance	Fructose
0	67	0
60	127	64
120	121	..
180	114	44
240	65	..

Epinephrine curve normal; administration of insulin did not affect fructose tolerance curve

TABLE 1.—*Data for Cases of Essential Fructosuria in the Literature—Continued*

Author	Patient	Urine: Reducing Substance	Urine: Levorotation	Urine: Seliwanoff Reaction	Urine: Yeast Fermentation	Urine: Methylphenyl Fructosazone	Urine: Reducing Substance with Sugar-Free Diet	Comment
Steinitz, H.: Deutsches Arch. f. klin. Med. **171**: 401, 1931	87 year old man	11.6% of ingested fructose excreted	Present	Positive	Positive	..	Absent	Dextrose and galactose tolerance curves normal. Results of fructose tolerance tests§ (100 Gm. given by mouth):

Minutes After Ingestion	Sugar in Urine, Gm. per 100 Cc.	Sugar in Blood, Mg. per 100 Cc.: Total Reducing Substance	Sugar in Blood, Mg. per 100 Cc.: Fructose
0	0	89	0
60	0.59	129	50
120	3.04	121	55
180	1.20	120	60
240	0.74	...	..

8 Gm. given by vein:

Minutes After Ingestion	Sugar in Blood, Mg. per 100 Cc.: Total Reducing Substance	Sugar in Blood, Mg. per 100 Cc.: Fructose
0	94	0
4	98	30
12	106	22
30	90	14
45	69	14
75	88	14

Renal concentration and dilution test showed specific gravity varying from 1.001 to 1.025

Examination of blood showed (mg. per 100 cc.):

Nitrogen	25
Calcium	10.6
Potassium	20.0
Phosphorus	3.8
Chlorides	360-328
Cholesterol	238-285
Bilirubin	0.64

Soisalo [10] (1933)	(1) 30 year old Finnish woman	7 to 15.6% of fructose excreted whether taken by mouth or by vein	Present	Positive	..	Phenyl fructosazone	Absent	Normal galactose and dextrose tolerance curves; administration of insulin did not change percentage of fructose excreted. Results of fructose tolerance test (52 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. Minutes After Ingestion / Total Reducing Substance / Fructose 0 / 94 / 0 30 / 130 / 9 60 / 144 / 16 120 / 128 / 21 180 / 107 / 6 Respiratory quotient: Fasting..... 0.73 1 hour after fructose..... 0.79 2 hours after fructose..... 0.75
	(2) 6 year old daughters of patient 1	Present	Present	Positive	..	..	Absent	
	(3) 19 year old Finnish girl	10.5 to 13.4% of fructose ingested excreted in urine whether given alone, with dextrose or as sucrose	Present	Positive	..	Phenyl fructosazone	Absent	Normal galactose and dextrose tolerance curves; administration of insulin did not affect amount of fructose excreted. Results of fructose tolerance test (70 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. Minutes After Ingestion / Total Reducing Substance / Fructose 0 / 94 / 0 15 / 96 / .. 30 / 109 / .. 45 / 125 / .. 60 / 132 / 20 90 / 135 / .. 120 / 133 / 18 180 / 120 / 12 Respiratory quotient: Fasting..... 0.63 1 hour after fructose..... 0.67 2 hours after fructose..... 0.67

TABLE 1.—*Data for Cases of Essential Fructosuria in the Literature—Continued*

Author	Patient	Urine: Reducing Substance	Urine: Levorotation	Urine: Seliwanoff Reaction	Urine: Yeast Fermentation	Urine: Methylphenyl Fructosazone	Urine: Reducing Substance with Sugar-Free Diet	Comment
Silver and Reiner[3] (1934).....	(1) 22 year old man	16% of total fructose ingested excreted in urine	Present	Positive	Positive	Formed	Absent	Dextrose and galactose tolerance curves normal; administration of insulin did not affect fructose tolerance curve. Results of fructose tolerance test (50 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. — Minutes After Ingestion: 0 — Total Reducing Substance: 90 — Fructose: 0; 60: 110: 45; 120: 115: 55; 180: 95: 20. Van den Bergh reaction, icteric index and results of bromsulfalein tests all within normal limits
	(2) 12 year old brother of patient 1	Present	Present	Positive	Positive	Formed	Absent	
	(3) 17 year old girl	Present	Present	Positive	Positive	Formed	Absent	
Zeghauser, A., and Lauterstein, A.: Polska gaz. lek. **14**: 931, 1935	43 year old woman	Present	0.1%	Positive	Positive	..	..	Dextrose tolerance curve normal
*Exton, W. G.: New York State J. Med. **36**: 1545, 1936	47 year old man	Present	..	..	..	..	..	Dextrose tolerance curve normal

van Lookeren Campagne, J.: Maandschr. v. kindergeneesk. **5**: 335, 1936	6½ year old Dutch boy	Present	Present	Positive	..	..	Absent	Dextrose tolerance curve normal. Results of fructose tolerance test (25 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. Minutes After Ingestion: 0, 30, 60, 90, 120, 150 Total Reducing Substance: 117, 134, 176, 162, 135, 124 Fructose: 24, 46, 86, 64, 55, 42 Administration of insulin had no effect on fructose tolerance curve, but 8 units caused a marked hypoglycemic reaction
Oster, K.: Monatschr. f. Kinderh. **67**: 155, 1936	8 year old girl	8.0%	Present	Positive	Positive	..	Absent	Dextrose tolerance curve normal. Results of fructose tolerance test (20 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. Minutes After Ingestion: 0, 30, 50, 85, 130, 180 Total Reducing Substance: 80, 115, 122, 106, 103, 114 Fructose: 0—, 48, 42, 36, 15, 3
Marble, A., and Smith, R. M.: J. A. M. A. **106**: 24 (Jan. 4) 1936	20 year old Jewish woman	2.97%	2.40%	Positive	Positive	Formed	..	Dextrose tolerance curve normal. Results of fructose tolerance test (40 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. Minutes After Ingestion: 0, 30, 60, 120, 180 Sugar in Urine, Gm. per 100 Cc.: 0, 2.4, 6.4, 4.2, 2.0 Total Reducing Substance: 88, 108, 114, 110, 92 Fructose: 0, 27, 45, 34, 16

TABLE 1.—*Data for Cases of Essential Fructosuria in the Literature—Continued*

Author	Patient	Urine: Reducing Substance	Urine: Levorotation	Urine: Seliwanoff Reaction	Urine: Yeast Fermentation	Urine: Methylphenyl Fructosazone	Urine: Reducing Substance with Sugar-Free Diet	Comment
Paisseau, G.; Ferroir, J., and Mangeat, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **53**: 1001, 1937	5 year old child	17.85% of fructose ingested excreted	Present	Positive	Positive	..	..	Dextrose tolerance curve normal
*Blatherwick, N. R., in Blumer, G.: The Practitioner's Library of Medicine and Surgery, New York, D. Appleton-Century Company, Inc., 1938, vol. 13, p. 264	(1) 28 year old Hungarian woman	Present; excreted 7.3 Gm. of fructose in 3 hours	..	..	..	..	..	After administration of 50 Gm. of fructose dextrose content of blood fell and fructose level rose
	(2) 24 year old brother of patient 1	Present	..	..	..	..	..	After administration of 50 Gm. of fructose dextrose content of blood fell and fructose level rose
Edhem, Erden and Steinitz[12] (1938)	22 year old woman	Present	Present	Positive	Positive	..	..	Dextrose tolerance curve normal. Results of fructose tolerance test (50 Gm. given by mouth):

Minutes After Ingestion	Sugar in Urine, Gm. per 100 Cc.	Sugar in Blood, Mg. per 100 Cc.: Total Reducing Substance	Sugar in Blood, Mg. per 100 Cc.: Fructose	Sugar in Blood, Mg. per 100 Cc.: Lactic Acid
0	0	95	0	8.1
30	0.62	101	28	9.0
60	1.63	127	42	8.2
120	2.80	70	26	8.4
180	2.02	96	11	9.1

Author	Patient	Urine: Reducing Substance	Urine: Levorotation	Urine: Seliwanoff Reaction	Urine: Yeast Fermentation	Urine: Methylphenyl Fructosazone	Urine: Reducing Substance with Sugar-Free Diet	Comment
Huber, J.; Lièvre, J. A.; Neret, W., and Illaire, E. F.: Bull. et mém. Soc. méd. d. hôp. de Paris **54**: 560, 1938	6 year old girl	1 to 2.25 Gm. per 100 cc.	Present	Positive	Positive	..	Absent	Dextrose and galactose tolerance curves normal
Rivoire, R., and Bermond, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **54**: 1049, 1938	40 year old Italian woman	30 to 60 Gm. per 24 hours	Present	Positive	Positive	..	..	Dextrose tolerance curve normal. Results of fructose tolerance test:

Minutes After Administration of Sugar	Sugar in Blood, Gm. per 100 Cc.: Dextrose	Sugar in Blood, Gm. per 100 Cc.: Fructose
0	100	0
60	63	58
120	90	44
180	92	18

Steinitz, H.: Gastroenterologia **64** : 334, 1939	(1) 5 year old Jewish boy	Present	Present	Positive	Positive	..	Absent	Dextrose tolerance curve normal. Results of fructose tolerance test (28 Gm. given by mouth): Sugar in Blood, Mg. per 100 Cc. Minutes After Ingestion: 0 / 45 / 90 / 120 Total Reducing Substance: 105 / 147 / 134 / 110 Fructose: 0 / 58 / 48 / 32
	(2) 3 year old brother of patient 1	Present	Present	Positive	Positive	..	Absent	
Jacobsen, V. C.: Am. J. M. Sc. **200** : 304, 1940	(1) 14 year old Jewish boy	Present	Present	Positive	Positive	..	..	Dextrose tolerance curve normal. Results of fructose tolerance test (56 Gm. given by mouth): Minutes After Ingestion: 0 / 30 / 120 / 180 Sugar — Urine, Gm. per 100 Cc.: 0 / 0.5 / 0.8 / 1.9 Sugar — Blood, Mg. per 100 Cc.: 84 / 109 / 127 / 117
	(2) 20 year old brother of patient 1	Present	Present	Positive	..	..	..	Dextrose tolerance curve normal. Results of fructose tolerance test (56 Gm. given by mouth): Minutes After Ingestion: 0 / 30 / 60 / 120 Sugar — Urine, Gm. per 100 Cc.: 0 / 0.34 / 1.05 / 3.15 Sugar — Blood, Mg. per 100 Cc.: 80 / 106 / 107 / 133
‖Lasker [4] (1941)	(1) 49 year old Jewish-Russian man	Present; 8 to 11% of ingested fructose excreted	Present	Positive	Positive	..	Absent; also absent after ingestion of 75 Gm. of dextrose	The rate of reduction at different temperatures ¶ was used as a test for fructose in all 7 cases reported by Lasker

TABLE 1.—*Data for Cases of Essential Fructosuria in the Literature—Continued*

Author	Patient	Urine						Comment
		Reducing Substance	Levo-rotation	Seliwanoff Reaction	Yeast Fermentation	Methylphenyl Fructosazone	Reducing Substance with Sugar-Free Diet	
	(2) 45 year old Jewish Russian man	Present	Present	Positive	Positive	..	..	
	(3) 18 year old Jewish Russian-American boy	Present	Present	Positive	Positive	..	..	
	(4) 8 year old Jewish Russian-American boy	Present	Present	Positive	Positive	..	..	
	(5) 22 year old Jewish Greek-American woman	Present	Present	Positive	Positive	..	..	
	(6) 35 year old Irish-American man	Present	Present	Positive	Positive	..	Absent; also absent after administration of 75 Gm. of dextrose	
	(7) 37 year old Irish-American man	Present	Present	Positive	Positive	..	Absent after administration of 75 Gm. of dextrose	

* Insufficient data are given to confirm the diagnosis.
† The urinalysis was done by Külz (Ztschr. f. Biol. **9**: 228, 1890).
‡ This author also reported another case in which there were both fructosuria and glycosuria.
§ The results of several tolerance tests are given; only the most typical are reproduced here.
‖ Some of the information given here was obtained through correspondence with the author.
¶ Lasker, Margaret, and Enklewitz, Morris: J. Biol. Chem. **101**: 289, 1933.

the diseases or complaints associated with fructosuria in the individual cases reported and has found that no single disorder is common to even a small number of cases.

Since the work of Isaac,[5] in which the perfused liver was shown to form glycogen from fructose, and the work of Ishimori [6] were reported

TABLE 2.—*Evidence for the Diagnosis of Essential Fructosuria in Cases 1 and 2*

	By Reduction *	By Optical Rotation †	By Fermentation ‡	Seliwanoff Reaction §	Melting Point of Methylphenyl Fructosazone ‖
Case 1.....	1.6%; after fermentation, trace; with fructose-free diet, trace	1.5%; after fermentation, 0; with fructose-free diet, 0	1.4%	Positive Negative Negative	153 C.
Case 2.....	2.0%; after fermentation, trace; with fructose-free diet, trace	2.2%; after fermentation, 0; with fructose-free diet, 0	1.8%	Positive Negative Negative	153 C.

* Roe, J. H.: J. Biol. Chem. **107**: 15, 1934.
† Koch, F. C.: Practical Methods in Biochemistry, Baltimore, William Wood & Company, 1937, p. 21.
‡ Koch, p. 221.
§ Koch, p. 15.
‖ Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 66.

TABLE 3.—*Results of Sugar Tolerance Tests in Cases 1 and 2*

		Sugar in Blood, Mg. per 100 Cc.					
		A. G. (Case 1)		Normal Control		N. G. (Case 2)	
Test Substance	Time, Minutes After Ingestion	Total Reducing Substance *	Fructose †	Total Reducing Substance *	Fructose †	Total Reducing Substance *	Fructose †
Dextrose, 50 Gm. given orally	0	81	0	90	0	48	0
	30	145	0	167	0	109	0
	60	142	0	137	0	153	0
	120	103	0	130	0	100	0
Fructose, 50 Gm. given orally	0	73.3	0	57.9	0	46	0
	30	89.2	38.0	94.1	13.4	69.2	14.5
	60	131.2	61.6	83.5	16.4	80.0	27.1
	120	100.4	52.0	78.3	8.4	143.0	30.9
	180	85.9	22.2	81.6	7.8	87.6	20.1

* Folin, O., and Wu, H.: J. Biol. Chem. **41**: 367, 1920.
† Roe, J. H.: J. Biol. Chem. **107**: 15, 1934.

it has been generally accepted that the liver converts fructose to glycogen readily. It is, nevertheless, manifestly unjust to accuse the liver of dysfunction when some abnormality of the intermediary metabolism of fructose is noted.

5. Isaac, S.: Ueber die Umwandlung von Lävulose in Dextrose in der künstlich durchströmten Leber, Ztschr. f. physiol. Chem. **89**:78, 1914.

6. Ishimori, K.: Ueber die Aufspeicherung und Abgabe des Glykogens, Biochem. Ztschr. **48**:332, 1913.

Because of the prevailing concept of the role of the liver in fructose metabolism, various tests of hepatic and renal function were carried out, the results of which are presented in table 4. As can easily be seen, all of the values for the function tests are well within normal limits. It is possible of course that either the liver or the kidney was primarily responsible for the faulty metabolism of the fructose and yet showed normal results for the various tests which were performed. We felt, however, that the explanation for the abnormal fructose metabolism might lie elsewhere.

TABLE 4.—*Results of Tests of Renal and Hepatic Function in Cases 1 and 2*

	Result	
	Case 1	Case 2
Procedure		
Galactose tolerance test *	Normal	Normal
Takata-Ara test †	Normal	Normal
Bromsulphalein test ‡	After 5 minutes, 75% of dye present in serum; after 30 minutes, none present	After 5 minutes, 90% of dye present in serum; after 30 minutes, none present
Examination of blood:		
Fibrinogen,§ Gm. per 100 cc	0.319	0.210
Phosphatase,‖ Bodansky units per 100 cc	10	11
Nonprotein nitrogen,¶ Mg. per 100 cc	32	28
Creatinine clearance test,# Mg. per 100 cc	15.25	5.31
Resorption of fluid	92.1%	97.0%

* Althausen, T. L.; Lockhart, J. C., and Soley, M. H.: Am. J. M. Sc. **199**: 342, 1940.

† Gradwohl, R. B. H.: Clinical Laboratory Methods and Diagnosis, ed. 2, St. Louis, C. V. Mosby Company, 1938, p. 637.

‡ Rosenthal, S. M., and White, E. C.: J. A. M. A. **84**: 1112 (April 11) 1925.

§ Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, ed. 11, Philadelphia, P.Blakiston's Son & Co., 1937, p. 453.

‖ Bodansky, A.: J. Biol. Chem. **101**: 93, 1933.

¶ Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 516.

Popper, H.; Mandel, E., and Mayer, H.: Biochem. Ztschr. **291**: 354, 1937. Dubos, R., and Miller, B. F.: J. Biol. Chem. **121**: 429, 1937. Dr. G. Ekstein performed the creatinine clearance test. The normal value is given as 95 to 96 per cent.

It has been known for some time that after the ingestion of fructose by normal human subjects a rise in the respiratory quotient occurs. The rise is more prompt and the respiratory quotient reaches a higher level than when dextrose is given.[7] Bachman and Haldi [7c] have shown that after the administration of fructose the respiratory quotient goes above 1. The explanation of this observation is still a matter of dispute.

7. (*a*) Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1932, vol. 2. (*b*) Deuel, H. J., Jr.: Intermediary Metabolism of Fructose and Galactose, Physiol. Rev. **16**:173 (April) 1936. (*c*) Bachmann, G., and Haldi, J.: Comparative Study of Respiratory Quotient Following Ingestion of Glucose and Fructose as Affected by Lactic Acid and Carbon Dioxide Changes in Blood, J. Nutrition **13**:157 (Feb.) 1937.

The most recent work seems to show that this high rise may be due to a greater accumulation of lactic acid in the blood after the ingestion of fructose. After the ingestion of dextrose there is little increase in the lactic acid of the blood.[8]

Respiratory quotients have been obtained in cases of essential fructosuria by several workers in the field.[9] Soisalo [10] found that in 2 cases of essential fructosuria the respiratory quotient changed but slightly from that of the fasting level after the ingestion of fructose. Heeres and Vos [11] made similar observations in their case of fructosuria. If the respiratory quotient is to be used as an index of the oxidation of a sugar, these observations point to a failure somewhere in the oxidative process.

Since it has been postulated that a rise in the level of lactic acid in the blood causes a rise in the respiratory quotient, our next step was to determine the change, if any, in the amount of lactic acid in the blood after the ingestion of fructose in our 2 cases.

Table 5 presents data for normal controls and for our 2 patients with essential fructosuria. This experiment clearly demonstrates that whereas for the 2 normal subjects there was an appreciable rise in the level of lactic acid in the blood after the ingestion of fructose, neither of our 2 patients with fructosuria showed a similar increase.

The only observation made previously on the level of lactic acid in the blood in a case of essential fructosuria was that in a case reported by Edhem, Erden and Steinitz.[12] They similarly found no increase in the level of lactic acid in the blood but drew no conclusions from this observation.

Our hypothesis is that the mechanism for the production of essential fructosuria lies in a failure of part of the ingested fructose to be broken

8. (*a*) Campbell, W. R., and Maltby, E. J.: Significance of Respiratory Quotients After Administration of Certain Carbohydrates, J. Clin. Investigation **6**:803 (Oct.) 1928. (*b*) Carpenter, T. M., and Lee, R. C.: Effect of Glucose and of Fructose on Human Respiratory Quotient and Alveolar Air, J. Nutrition **6**:55 (Jan.) 1933. (*c*) Bachmann and Haldi.[7c]

9. Respiratory quotients were obtained for both of our patients, but because of the technical difficulties which were encountered, the results cannot be reported.

10. Soisalo, P.: Ueber die essentielle Fruktosurie, Acta Soc. med. fenn. duodecim **14**:1, 1933.

11. Heeres, P. A., and Vos, H.: Fructosuria: Report of Case, Arch. Int. Med. **44**:47 (July) 1929.

12. Edhem; Erden, F., and Steinitz, K.: Études sur un cas de lévulosurie essentielle, Acta med. Scandinav. **97**:455, 1938.

down to lactic acid. We further hypothesize that in normal human beings about 80 per cent of the ingested fructose is converted to glycogen, the remainder being broken down to lactic acid. In our cases, as well as in those of Heeres and Vos,[11] Barrenscheen [13] and others, 10 to 20 per cent of the total amount of fructose ingested was excreted as such in the urine instead of being metabolized. This hypothesis would account for the failure of a normal increase in the concentration of lactic acid in the blood and rise in the respiratory quotient. The abnormality may lie in the failure or lack of some specific enzymatic action, the site of which has not yet been determined but which may be in the intestine, the blood or the liver.

TABLE 5.—*Results of Fructose Tolerance Tests in Cases 1 and 2* *

Subject	Time, Minutes After Ingestion of Fructose	Constituents of Blood, Mg. per 100 Cc.			
		Total Reducing Substance †	Fructose ‡	Inorganic Phosphorus §	Lactic Acid ‖
Normal control 1.....	0	87	0	5.3	12.5
	30	117	7.9	5.2	20.0
	65	113	1.2	5.0	26.0
Normal control 2.....	0	91	0	5.5	17.2
	30	116	3.7	5.4	22.6
	65	112	4.6	5.7	29.4
A. G. (case 1).....	0	96	0	5.4	16.4
	30	128	42.5	5.5	17.5
	65	129	17.8	6.0	18.2
N. G. (case 2).....	0	...	0	4.9	12.4
	30	132	31.5	5.0	12.1
	65	138	13.6	5.4	12.6

* Fifty grams of fructose was given by mouth for each test.
† Folin, O., and Wu, H.: J. Biol. Chem. **41**: 367, 1920.
‡ Roe, J. H.: J. Biol. Chem. **107**: 15, 1934.
§ Fiske, C. H., and Subbarrow, Y.: J. Biol. Chem. **66**: 375, 1925.
‖ Elgart and Harris, J. S.: Indust. & Engin. Chem. **12**: 758, 1940.

SUMMARY

The cases of 2 Jewish brothers, 6 and 9 years old, with essential fructosuria are reported. Data are presented showing conclusively that the observations in these 2 cases meet all the criteria of essential fructosuria. A tabular review of the literature on this subject is given.

Experimental data are presented to support our hypothesis that in cases such as those reported the mechanism for the fructosuria lies in the failure of ingested fructose to be broken down to lactic acid, as it is in normal subjects.

NOTE.—Subsequent to the preparation of this article there appeared an abstract of an article by Sterkin and Vengerova [14] in which the

13. Barrenscheen, H. K.: Ueber Fructosurie, Biochem. Ztschr. **127**:222, 1922.
14. Sterkin, E. Y., and Vengerova, F. M.: The Role of the Liver in Fructose Metabolism After Angiostomy by E. S. London's Method, Bull. biol. et méd. expér. URSS; abstracted, Chem. Abstr. **35**:6635 (Oct. 10) 1941.

authors showed experimentally that in normal dogs approximately 20 to 30 per cent of the ingested fructose is secreted by the liver in the form of lactic acid.

There also appeared a paper by Rynbergen, Chambers and Blatherwick [15] on the respiratory metabolism in fructosuria. Their studies were made on 4 patients with fructosuria previously reported on, 2 by Blatherwick and 2 by Silver and Renier, and the cases are included in table 1 of this article. Their results show that after the ingestion of fructose by these patients the blood lactic acid rose only slightly and that the respiratory quotient was comparable to that which occurs after ingestion of dextrose, in contradistinction to the rise above unity found in normal patients after ingestion of fructose.

The experimental results in these two papers are added confirmation of the validity of our hypothesis.

Dr. Benjamin Kramer gave help and guidance and Dr. C. S. Byron, Dr. S. Michalover, Mr. Henry Leonard and Mr. Alexander Wienerman technical assistance in this study.

15. Rynbergen, H. J.; Chambers, W. H., and Blatherwick, N. R.: J. Nutrition **21**:553 (June 10) 1941.

CREATINE METABOLISM IN HYPOTHYROID INFANTS AND CHILDREN

FURTHER OBSERVATIONS

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In 1934 [1] a detailed study of the creatine metabolism in 2 hypothyroid children was published. It was concluded that the physiologic creatinuria, which may be absent or markedly diminished in the hypothyroidism of childhood, is restored to levels observed for normal children by treatment with thyroid. The establishment and maintenance of the creatinuria of the cretins previously reported on appeared to be a finding of diagnostic value as well as a means of judging adequacy of therapy.

Two groups of investigators have stated the belief that the effect of continuous administration of thyroid in increasing the creatine excretion of hypothyroid children is not long continued. Shorr, Richardson and Mansfield [2] have questioned the permanency of the restored creatinuria produced by uninterrupted thyroid therapy in the 2 hypothyroid children reported on in the aforementioned earlier paper.[1] They inferred that the observed creatinuria resulting from the thyroid therapy might be explained on the basis of what they considered abnormally high basal metabolic rates [3] or by a temporary adjustment to thyroid treatment, such as occurs in adults. Wilkins, Fleischmann and Block [4] recently

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1. Poncher, H. G.; Visscher, M. B., and Woodward, H.: Creatine Metabolism in Children with Hypothyroidism, J. A. M. A. **102**:1132 (April 7) 1934.

2. Shorr, E.; Richardson, A. B., and Mansfield, J. S.: Influence of Thyroid Administration on Creatine Metabolism in Myxedema of Adults, Proc. Soc. Exper. Biol. & Med. **32**:1340, 1935.

3. Shorr, E.: Personal communication to the authors.

4. Wilkins, L.; Fleischmann, W., and Block, W.: Hypothyroidism in Childhood: II. Sensitivity to Thyroid Medication as Measured by the Serum Cholesterol and the Creatine Excretion, J. Clin. Endocrinol. **1**:14, 1941.

stated that the increase in excretion of creatine by hypothyroid children receiving continuous thyroid therapy is of relatively short duration.

The purpose of this paper is threefold: first, to furnish additional evidence concerning the maintenance of the physiologic creatinuria of childhood that is initiated by thyroid treatment in cases of hypothyroidism; second, to discuss the application of the present day standards for basal metabolism of normal children to children of abnormal physical development; third, to show that in the patients whose basal metabolic

Fig. 1 (case 1).—A girl aged 5½ years with hypothyroidism: (*A*) before treatment and (*B*) after five weeks of treatment.

rates could not be determined, whose cholesterol levels were within the normal range and the roentgenologic appearance of whose epiphysial centers was not conclusive,[5] the absence or diminished level of creatinuria was a valuable adjunct in the diagnosis of hypothyroidism.

5. The osseous system may exhibit little or no change in patients who have received previous therapy or in whom the thyroid deficiency is of short duration.

EXPERIMENTAL STUDIES

Subjects.—The subjects for this study were 6 hypothyroid girls. Four of the 6 children (D. J., V. K., B. C. and E. S.[6]) were observed at various intervals throughout a period of continuous therapy with thyroid (earlier studies on 2 of these 4 subjects, D. J. and V. K., were presented in a previous paper [1]). Three of the children were infants (B. C., E. L. and G. E.), and their cases are included in this report to

Fig. 2 (case 2).—Patient with hypothyroidism at the age of 12 years.

substantiate our contention that the creatinuria response to administration of thyroid is of diagnostic value along with the clinical observations.

6. E. S. was the subject for another study, conducted to observe the effect of dietary protein on the level of creatinuria of the hypothyroid child. This deviation in the dietary control does not detract from the eligibility of E. S. as one of the subjects included in this investigation to show the persistence of an established creatinuria. We cannot, however, employ the data on her urinary preformed creatinine for information concerning the effect of thyroid therapy on the excretion of creatinine.

CASE 1.—D. J. was recognized elsewhere as a hypothyroid child at the age of 8 months, when she was given thyroid. When she was 18 months old the mother sought further aid, as she was dissatisfied wtih the child's progress. Her first teeth appeared at the age of about 1½ years, and she did not walk until she was 4 years old. Between the ages of 4 and 4½ years little or no treatment was given.

We saw D. J. at the age of 5½ years (fig. 1 *A*). She had supraclavicular fat pads, a waxy yellow skin and a large tongue. No thyroid tissue was palpable. After approximately five weeks of treatment the patient showed satisfactory improvement (fig. 1 *B*).

CASE 2.—V. K.[7] was first seen by us at the age of 12 years (fig. 2). At this time she exhibited some secondary sexual characteristics. Her physical development was fairly good, but her mental progress was poor (mental age, 6 years and 4 months; intelligence quotient, 54). The patient was of Polish extraction,

Fig. 3 (case 2).—Patient with hypothyroidism (fig. 2) between 1 and 2 years of age, when the condition was recognized.

and there was no family history of thyroid disturbance. Her first teeth appeared at the age of about 1 year. She sat up at the age of 3½ years, walked and spoke simple words at 4 years and talked in short sentences at 6 years. Her hypothyroidism was recognized between the ages of 1 and 2 years (fig. 3), at which time her skin was dry, her tongue was large and her fingers were stubbed. Her abdomen protruded, and an umbilical hernia was present. Examination of her eyes revealed strabismus and nystagmus. Treatment prior to her admission to this hospital was not adequate, owing to her mother's failure to cooperate with her physician. Since she has been under our care, her cooperation has been excellent, and the treatment has been continuous and adequate.

CASE 3.—E. S., of Polish extraction and the third of six children, at the age of 3 years was taken to a hospital because she did not walk or talk and because

7. V. K. was studied by permission of Dr. Harold Rosenbaum and the Children's Memorial Hospital.

no teeth were present. Prior to our seeing her she had about three months of thyroid therapy of unknown dosage.

When we first saw her, at the age of 13 years (fig. 4 *A*), the complaint being marked constipation, she weighed 37¾ pounds (17 Kg.) and was 37¾ inches (95 cm.) tall. Her intelligence quotient was 35, and her mental age was 5 years

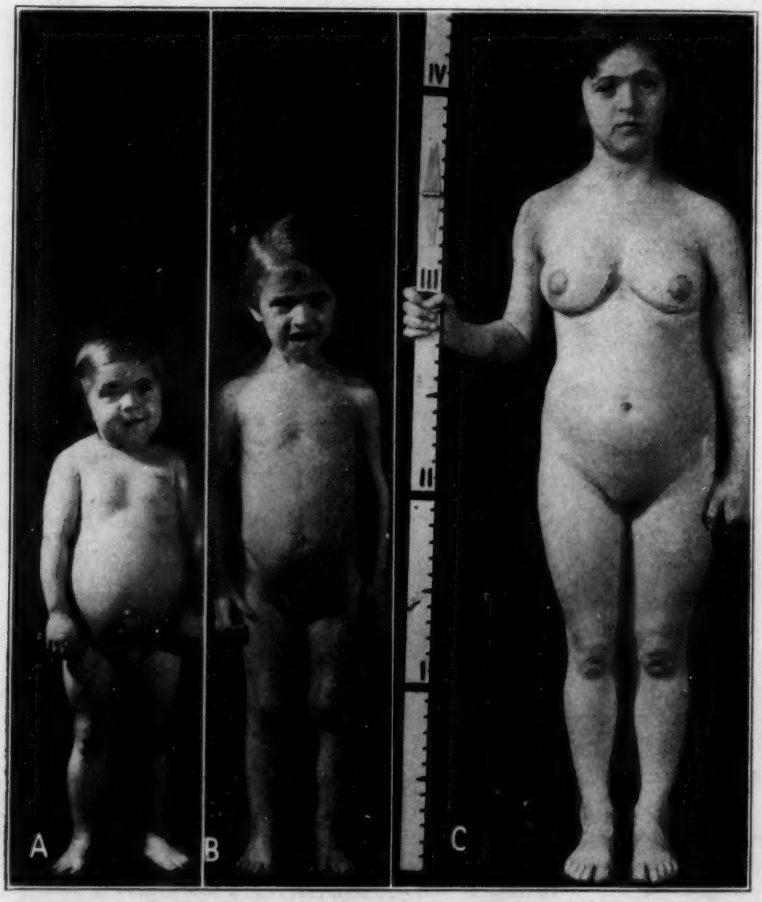

Fig. 4 (case 3).—Patient with hypothyroidism: (*A*) at the age of 13, on admission to the hospital; (*B*) after about seven months of therapy, and (*C*) at the age of 17.

and 2 months. Her skin was thick, and her hair was coarse. She had supraclavicular fat pads, a protruding abdomen and an umbilical hernia. Ossification at the wrist was like that of a 3 year old child. Figure 4 *B* shows her after about seven months of therapy. Figure 4 *C* shows her at the age of 17 years and gives one an idea of the clinical progress (height, 51½ inches [131 cm.]; weight, 68¾ pounds [31 Kg.]). She has made little progress in her mental development.

Fig. 5 (case 4).—Child aged 14 months with hypothyroidism.

Fig. 6 (case 4).—Child with hypothyroidism (fig. 5) after unsuccessful thyroid transplant (*A*) and after resumption of therapy (*B*).

CASE 4.—B. C. entered our institution at the age of 14 months. She had received no thyroid for some time (fig. 5). She exhibited a dry, coarse skin, a dull facial expression, thick lips, a large tongue, a large abdomen and an umbilical

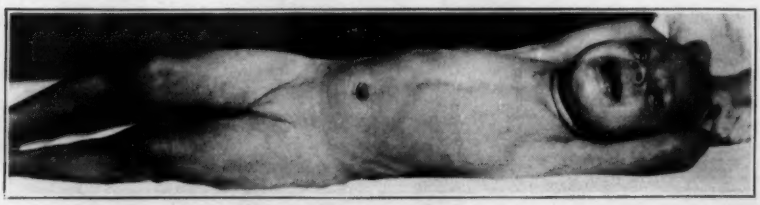

Fig. 7 (case 5).—Child with hypothyroidism, showing marked improvement after administration of thyroid.

Fig. 8 (case 5).—Child with hypothyroidism (fig. 7) when therapy was discontinued for research work.

hernia. At this time she had normal carpal development, for she had had therapy prior to our seeing her. On May 15, 1935 she had a thyroid transplant, which was unsuccessful, for the symptoms of thyroid deficiency returned (fig. 6*A*). Figure 6*B* shows the changes in this child after the resumption of therapy.

CASE 5.—E. L.,[8] a Negro child 10 months old, was brought to the Cook County Children's Hospital because of failure to grow and marked inactivity. Unfortunately no picture was taken when she was first admitted to the hospital. The child had an umbilical hernia, was not able to sit up and had no teeth. Roentgenograms revealed neither carpal nor distal femoral epiphyses. The administration of thyroid caused marked improvement (fig. 7). When we first saw the child therapy was discontinued for some preliminary research work (fig. 8). After the completion of these studies, thyroid was again administered and clinical progress was noted. We did not have the opportunity to observe her between these two reported experimental periods.

CASE 6.—G. E.[8] was admitted to our institution at the age of 8 months. There was no history of thyroid trouble in the family. Soon after birth the mother said

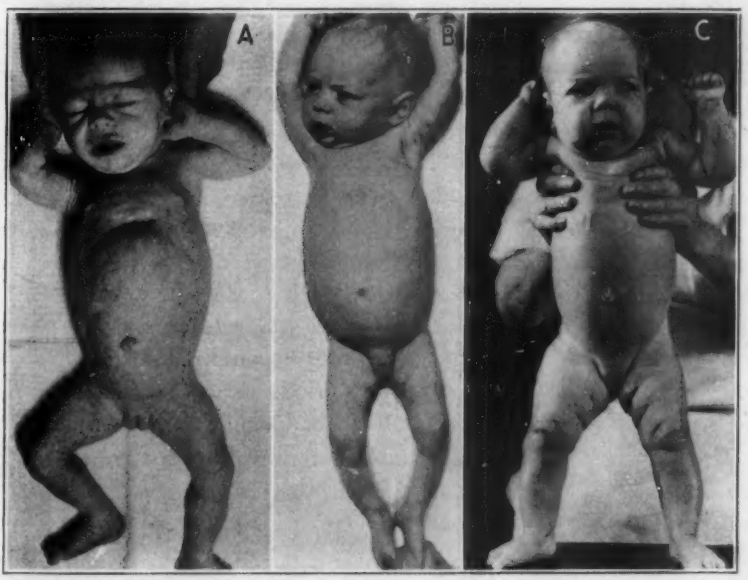

Fig. 9 (case 6).—Child with cretinism: (*A*) at the age of 5 months, when the diagnosis was made; (*B*) after administration of thyroid, and (*C*) showing retrogressive changes following discontinuance of thyroid administration.

the child exhibited a large tongue and abdomen and pallor and was markedly constipated. When she was first brought to the Cook County Children's Hospital, at the age of 5 months, the correct diagnosis of cretinism was made (fig. 9 *A*), and thyroid was given in increasing doses up to 1½ grains (0.1 Gm.) per day. Notable improvement followed (fig. 9 *B*). When we first saw the child the therapy was discontinued for research purposes, and retrogressive changes appeared (fig. 9 *C*). With the resumption of therapy improvement again followed.

Procedures.—Dietary control, procedures for collecting the urines and methods for determining the urinary creatine and creatinine of the

8. These patients were studied by permission of Dr. Joseph Greengard.

older children have been previously described.[1] Twenty-four hour specimens of urine were obtained from the infants by the use of a metabolism frame designed to collect quantitative outputs of excreta. The cholesterol levels were determined on whole blood by a modification of Bloor's method, as described by Levinson and MacFate.[9] A McKesson recording metabolar was used for the estimation of the children's basal heat production.

The creatinine and creatine eliminated by the 2 most recently observed subjects, infants E. L. and G. E., were ascertained by somewhat different methods which are applicable to a more modern and superior technic. Preformed creatinine was determined by the micromethod of Folin[10]; a micromodification of the autoclave procedure of Benedict and Myers[11] was used for the estimation of the total creatinine. Creatine values were estimated by subtracting the amount of preformed creatinine from the total and multiplying this difference by 1.16. Trinitrophenol was purified by Benedict's method.[12] A Cenco-Sheard photoelectric colorimeter was substituted for the ocular one formerly used.

Results and Comment.—Creatine and creatinine excretions of 6 hypothyroid children are summarized in table 1. Four of the subjects were readmitted to the hospital for subsequent studies. On two occasions, after an interval of nine months and then again three years after the initial study, D. J. was observed for experimental periods of fourteen days' duration. V. K. and B. C. were hospitalized for a subsequent study eight months after their first periods of observation, and E. S. was seen one and one-half years after treatment with thyroid.

Creatinuria[13]: The data in table 1 confirm our contention that the creatinuria established with thyroid therapy is persistent. During the final period of observation, all 3 of the older children (D. J., 8 years old; V. K., 13 years old, and E. S., 15 years old) showed creatine

9. Levinson, S. A., and MacFate, R. P.: Clinical Laboratory Diagnosis, Philadelphia, Lea & Febiger, 1937, p. 224.

10. Folin, O.: On the Determination of Creatine in the Urine, J. Biol. Chem. **17**:469, 1914.

11. Benedict, F. G., and Meyers, V. C.: The Determination of Creatine and Creatinine, Am. J. Physiol. **18**:397, 1907.

12. Benedict, S. R.: A Method for the Purification of Picric Acid for Creatinine Determinations, J. Biol. Chem. **54**:239, 1922.

13. Creatine tolerances (Richardson, H. B., and Shorr, E.: Relation of Thyroid Gland to Grave's Disease, M. Clin. North America **18**:791, 1934) were not always determined because of the difficulties in hospitalizing the children long enough to carry out the test. From our experience with creatine tolerance studies on children, we do not feel that, in general, this test is of sufficient value to be included. The results are often very confusing and unexplainable rather than elucidating. For these reasons the creatine tolerance studies that were performed are not included in the report of this investigation.

TABLE 1.—*Average Daily Values of Creatinine, Creatine and Cholesterol*

Subject	Date	Age, Yr.	Body Weight, Kg.	Diet	Thyroid per Day, Grains	Preformed Creatinine		Creatine		Total Creatinine		Nitrogen Coefficient			Cholesterol, Mg. per 100 Cc.	Roentgenograms
						Total, Mg.	Coefficient	Total, Mg.	Coefficient	Total, Mg.	Coefficient	Preformed	Creatine	Total		
D. J.	1933 3/13-20	5	19.0	General	None	403	21.2	0	0	403	21.2	7.88	0	7.88	263	Ossification of carpal centers normal; if anything, there was some premature ossification, as six carpal bones were visible (2/27/33)
	4/28-5/17	5	17.8	General	1½	302	17.0	286	16.1	549	30.9	6.32	5.98	11.49	208	
	1934 1/20-26 and 1/31-2/7	6	18.3	General	1½	256	14.0	160	8.7	394	21.5	5.2	3.23	7.99	238	
	1936 7/11-8/2	8	20.6	Meat-free	¾	354	17.2	147	7.2	481	23.4	6.39	2.68	8.70		
V. K.	1933 6/1-13	12	43.9	General	None	673	15.3	0	0	673	15.3	5.69	0	5.69	...	Wrists approximately normal for age (3/28/33)
	6/23-28	12	45.7	General	1-2	837	18.3	334	7.3	1,125	24.6	6.80	2.71	9.14	416	
	1934 3/12-18	13	49.4	General	3	679	13.7	304	6.1	941	19.0	5.09	2.27	7.06	185	
E. S.	1935 9/19-30	13	19.0	Meat-free	None	289	15.2	0	0	289	15.2	5.65	0	5.65	434	Wrists showed ossification approximating that of a 3 year old child; sella approximately normal (9/5/38)
	11/2-18	13	19.7	High protein	None	343	17.4	68	3.5	402	20.4	6.47	1.30	7.58	454	
	1936 1/2-9	13	18.0	High protein; beef extract 15 Gm. daily	2	296	16.4	332	18.4	582	32.3	6.10	6.84	12.01	156	
	1937 7/18-23	15	21.0	Meat-free	3	241	11.5	131	6.3	354	16.9	4.28	2.34	6.28		
B. C.	1933 11/14-22	Mo. 14	8.81	↑	None	126	14.3	1	0.1	127	14.4	5.32	0.04	4.72	250	Ossification approximately normal for age (10/30/33)
	12/14-17	15	8.83		½	156	17.7	22	2.6	175	19.9	6.58	0.97	7.40	250	
	12/20-22	15	8.70		1	134	15.4	96	11.0	217	24.9	5.72	4.09	9.26	208	
	1934 10/15-16	25	9.90		1	136	13.7	116	11.7	236	23.8	5.09	4.35	8.85	278	
E. L.	1938 5/12-14	10	4.0		None	26	6.5	2	0.6	28	7.0	2.42	0.22	2.60	176	Examination of cranium showed that both anterior and posterior fontanels were open and easily admitted one finger; roentgenograms of long bones showed an absence of carpal bones and of ossification centers at lower end of femurs (C. C. H.; 4/4/38); no ossification in carpal bones (9/29/38)
	9b22-24	14½	5.80		½ for 1 wk.	48	8.3	64	11.0	103	17.8	3.09	4.09	6.62	227	
				Infants' general diet (meat-free)												
G. E.	1939 9/11-13	12½	6.96		None	80	11.5	14	2.0	92	13.2	4.28	1.74	4.91	250	Ossification in two of carpal bones suggestive of precocious development (9/26/39)
	9/24-26	13	7.05		½ for 1 wk.	78	11.1	114	16.1	176	25.0	4.13	5.98	9.29		
	10/1-6	13	7.455		½ for 2 wk.	86	11.5	117	15.8	187	25.1	4.28	5.87	9.33		
	10/17-19	13½	7.88		1 for 1 wk.	84	10.7	132	16.7	198	25.1	3.98	6.21	9.33		
	10/28-31	14	8.238		1 for 2 wk.	86	10.4	88	10.7	162	19.6	3.87	3.98	6.02		
	11/7-9	14½	8.725		1 for 4 wk.	92	10.5	86	9.9	166	19.0	3.90	3.68	7.06		
	12/16-19	16	9.58	↓	1½ for 4 wk.	104	10.8	99	10.3	189	19.7	4.01	3.83	7.32		

coefficients of 7.2, 6.1 and 6.3 respectively; the total excretions of creatine were 147, 304 and 131 mg. per twenty-four hours respectively. These values are in accord with the findings of Wang and her associates [14] on girls of ages corresponding to those of our subjects and also with the upper level reported by Wilkins, Fleischmann and Block [15] on 17 control children. The data referring to the infant B. C. show that a small dose of thyroid was as effective in establishing the appearance of urinary creatine as it was in the 3 older children; the continuous administration of an adequate amount of thyroid raised the creatine content of the urine to an average daily level of 96 mg. These observations corroborate our earlier work and that reported by Beumer and Iseke.[16] Ten months later B. C. was readmitted for further studies. We observed that thyroid therapy had a continuous effect in maintaining the normal physiologic excretion of urinary creatine (11.7 mg. per kilogram). This level has been observed by other investigators [17] on normal subjects of the same age.

Since the substitution therapy with thyroid markedly increased the creatine excretion of these subjects, the authors felt justified in concluding from the earlier report [1] that the observed creatinuria had been established by the daily administration of thyroid. These subsequent data have shown that creatinuria was present in 4 cases from eight months to three years after treatment was begun. Although there were instances of a decreased creatine level after prolonged treatment (table 1), there were no instances in which creatinuria was diminished to pretreatment values. The appearance of creatine in the urine subsequent to the administration of thyroid appeared to be the most indicative laboratory aid for the diagnosis of hypofunctioning thyroid glands. Creatinuria always began before any physical change or clinical improvement was apparent.

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14. (*a*) Wang, C. C.; Genther, I., and Hogden, C.: Metabolism of Adolescent Girls: III. The Excretion of Creatine and Creatinine, Am. J. Dis. Child. **51**:1 (Jan.) 1936. (*b*) Wang, C. C.: Basal Metabolism and Preformed and Total Creatinine in Urine of Seventy Children, ibid. **57**:838 (April) 1939.

15. Wilkins, L.; Fleischmann, W., and Block, W.: Hypothyroidism in Childhood: I. The Basal Metabolic Rate, Serum Cholesterol and Urinary Creatine Before Treatment, J. Clin. Endocrinol. **1**:3, 1941.

16. Beumer, H., and Iseke, C.: Der Kreatin-Kreatininstoffwechsel bie Myxödem und Gesunden unter Einwirkung von Thyreoidin, Berl. klin. Wchnschr. **57**:178, 1920.

17. (*a*) Garot, L.: L'excretion des corps créatiniques chez le nourrisson sain, Compt. rend. Soc. de biol. **101**:1457, 1929. (*b*) Rougichitch, O. S.: The Creatine Coefficient in the Infant, Arch. Dis. Childhood **1**:289, 1926. (*c*) Denis, W., and Kramer, J. G.: The Influence of Protein Intake on Creatine Excretion in Children, J. Biol. Chem. **30**:189, 1917. (*d*) Gamble, J. L.: A Study of Creatinuria in Infants, ibid. **40**:215, 1919. (*e*) Stearns, G.: Personal communication to the authors.

Preformed Creatinine: The discussion of the influence of thyroid therapy on the urinary excretion of creatinine is limited at present to subjects D. J. and V. K. B. C. will be mentioned in the section of this paper in which the hypothyroid infants are discussed. The dietary regulations used on subject E. S. for another study do not permit us to include our observations on her urinary preformed creatinine when thyroid was administered.

D. J.'s level of urinary preformed creatinine as well as of urinary creatine was altered by the ingestion of thyroid (table 1).[18] When thyroid was given, D. J. on a diet containing meat had a decrease in the excretion of creatinine. From an initial daily value of 403 mg., her average levels for preformed creatinine were reduced to 302 and 256 mg. per day during two subsequent periods of observation that were nine months apart. Fan [19] noted this same response to thyroid therapy in his recently reported investigations on 3 cretins. Wilkins [15] found that the creatinine content of the urine was reduced in only 1 of the 14 hypothyroid children he observed. These experimental results as well as those reported by Fan and Wilkins indicate that urinary creatinine may not be refractory to thyroid therapy. These observations are not in accord with the belief of Talbot, Worcester and Stewart [20] that the level of creatinine excreted in the urine is not affected by activity of the thyroid gland.

Fan [19] has interpreted this observed reduction in creatininuria as a result of the depleting effect of ingested thyroid on the stores of body creatine. He gave this explanation on the basis of the work of Benedict and Osterberg,[21] who conclusively showed that creatinine formation is influenced by the availability of creatine in the body. Fan's interpretation may also be invoked to explain D. J.'s diminished excretion of creatinine with thyroid treatment.

In contrast to D. J., V. K. excreted greater amounts of creatinine when she first received thyroid therapy. The initial average level of 673 mg. per day was increased during the administration of thyroid

18. In a previous communication [1] we reported that thyroid therapy had no appreciable effect on the preformed creatinine eliminated by D. J. and V. K. A continuation of the observations earlier reported on D. J., along with further experience in creatine and creatinine studies, has revealed a definite influence on the urinary preformed creatinine in the subject D. J.

19. Fan, C.: Creatine and Creatinine Metabolism in Hypothyroidism, J. Pediat. **18**:57, 1941.

20. Talbot, N. B.; Worcester, J., and Stewart, A.: New Creatinine Standards for Basal Metabolism and Its Clinical Application, Am. J. Dis. Child. **58**:506 (Sept.) 1939.

21. Benedict, S. R., and Osterberg, E.: Studies in Creatine and Creatinine Metabolism: V. The Metabolism of Creatine, J. Biol. Chem. **56**:229, 1923.

to 837 mg. This increase was most likely due to the fact that eight days before she received thyroid her creatine tolerance was determined. She ingested 3 Gm. of creatine daily for six successive days and retained 73.9 per cent of this amount. During thyroid therapy a large proportion of this additional reserve of creatine unquestionably was excreted as creatinine as well as creatine. Had we had the opportunity to prolong the hospitalization of this child, we might have observed a diminished level of her urinary creatinine with continuous therapy.

The differences in the chronologic and physiologic ages of D. J. and V. K. raises a question concerning a similarity in the influence of thyroid medication on the levels of creatinine excreted by these 2 children. D. J. was 5 years old, whereas V. K. was 12 years of age and exhibited some secondary sexual development. One must therefore consider the possibility of a difference in the effects that thyroid therapy may bring about in the endocrine system of a young child who does not exhibit the physiologic effects of puberty and of an older child who is definitely in the pubescent age. It is possible that in the subject V. K. the administration of thyroid would alter the activities of the anterior lobe of the pituitary body and the ovaries, which in turn would augment the level of creatinine in the urine. There is experimental evidence from the work of Schrire and Zwarenstein [22] and from our own unpublished work [23] that anterior pituitary extracts have brought about an increased level of urinary creatinine. Estrogens have also been shown to increase the creatinine metabolism through the anterior lobe of the pituitary body.[24] Nathanson and his collaborators [25] have found a close correlation between the urinary excretions of creatinine and the 17-keto steroids in growing boys and girls. These authors state that the most likely explanation of this close correlation appears to be that androgens exert an influence on the muscle mass of the subject. An increase of androgen formation, therefore, would result in increased muscle mass and thereby augment the level of creatininuria.

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22. Schrire, I., and Zwarenstein, H.: The Influence of the Gonads on Protein Metabolism: III. The Effect of Injections of Anterior Pituitary Extracts on Urinary Creatinine in Normal and Castrated Rabbits, Biochem. J. **27**:1337, 1933.

23. In a Lorain-Levi dwarf to whom we administered an anterior pituitary extract containing the growth-promoting factor there was a definite increase in preformed creatinine from an average daily level of 239 mg. to one of 363 mg.

24. Schrire, I., and Zwarenstein, H.: Influence of the Gonads on Protein Metabolism: II. The Effect of Ovariectomy and of Injections of Gonadal and Anterior Pituitary Extracts on Urinary Creatinine in Female Rabbits, Biochem. J. **28**:356, 1934.

25. Nathanson, I. T.; Miller, R. B.; Towne, L. E., and Aub, J. C.: The Close Correlation of Androgen and Creatinine Excretion in Normal Children, Endocrinology **28**:866, 1941.

Cholesterol: Hypercholesteremia, which frequently exists with hypothyroidism, was shown only by the 2 subjects V. K. and E. S. The elevated values for cholesterol ranged from 416 to 454 mg. per hundred cubic centimeters of blood. These figures are considerably less than those reported by Wilkins, Fleischmann and Block [15] (660 mg.) and Bronstein [26] (782 mg.). The pretreatment values of cholesterol for D. J. and B. C. (263 and 250 mg., respectively) were not abnormally high.

Wilkins, Fleischmann and Block [4] considered the effect of daily oral administration of thyroid or injection of a single dose of thyroxin on the serum cholesterol a better means of differentiating the hypothyroid from the normal child than the change in the amount of creatine excreted in the urine. He found that after the injection of a single dose of 5 mg. of thyroxin, the hypothyroid child displayed a decrease in the serum cholesterol amounting to 120 to 229 mg. per hundred cubic centimeters. The effect lasted from thirty-two to seventy-one days before the cholesterol returned to its previous level. In the normal children observed by Wilkins and his co-workers, the same dose of thyroxin caused only a slight and transient effect; the concentration of cholesterol decreased only 16 to 47 mg. per hundred cubic centimeters and returned to the previous level within six to thirteen days. These investigators reported that the creatine excretion subsequent to the injection of thyroxin showed less difference between the hypothyroid and control groups because thyroxin did bring about an increased creatinuria in some normal children. Wilkins and Fleischmann [27] suggested the discontinuance of thyroid medication and the observance of the cholesterol concentration over a period of eight to twelve weeks when one is questioning a previous diagnosis of hypothyroidism.

Boyd and Connell [28] have reported that the estimation of plasma lipids is a convenient means of detecting mild hypothyroidism in adults.

Recently Radwin and his collaborators [29] suggested that the determinations of total serum lipids are of value in the diagnosis of borderline hypothyroidism in children. Since there was no overlapping between the ranges of total lipid concentrations in normal children and in children

26. Bronstein, I. P.: Studies in Cretinism and Hypothyroidism in Childhood: I. Blood Cholesterol, J. A. M. A. **100**:1661 (May 27) 1933.

27. Wilkins, L., and Fleischmann, W.: The Diagnosis of Hypothyroidism in Childhood, J. A. M. A. **116**:2459 (May 31) 1941.

28. Boyd, E. M., and Connell, W. F.: Thyroid Disease and Blood Lipids, Quart. J. Med. **5**:455, 1936.

29. Radwin, L. S.; Michelson, J. P.; Melnick, J., and Gottfried, S.: Blood Lipid Partition in Hypothyroidism of Children, Am. J. Dis. Child. **60**:1120 (Nov.) 1940.

TABLE 2.—*Basal Metabolic Rates*

Subject	Date	Age, Years	Height, Cm.	Weight, Kg.	Surface Area, Square Meter	Pulse Rate	Thyroid, Grains	Surface Area Standards: F. B. Talbot, 1921: Observed Calories per Square Meter	Surface Area Standards: F. B. Talbot, 1921: Average Calories per Square Meter	Surface Area Standards: F. B. Talbot, 1921: Per Cent Deviation	Surface Area Standards: Boothby, 1929: Average Calories per Square Meter	Surface Area Standards: Boothby, 1929: Per Cent Deviation	Height and Weight Standards: Observed Calories per Hr.	Height and Weight Standards: Height: F. B. Talbot, 1935: Average Calories per Hr.	Height and Weight Standards: Height: F. B. Talbot, 1935: Per Cent Deviation	Height and Weight Standards: Weight: F. B. Talbot, 1935: Average Calories per Hr.	Height and Weight Standards: Weight: F. B. Talbot, 1935: Per Cent Deviation	Creatinine Standard: N. B. Talbot, 1939: Observed Calories per 24 Hr.	Creatinine Standard: N. B. Talbot, 1939: Expected Calories per 24 Hr.	Creatinine Standard: N. B. Talbot, 1939: Per Cent Deviation
	1933																			
D. J.	3/20	5 5/12	99	19.7	0.700	76	0	36.34	↑	—13	↑	—30	25.44	↑	—16	↑	—28	611	1,002	—39
	3/22			19.7	0.700	68	0	31.49	|	—25	|	—39	22.05	|	—27	|	—38	529	949	—44
	3/24			19.9	0.700	63	0	31.14	|	—25	|	—40	21.80	|	—28	|	—38	523	918	—43
	3/29			19.8	0.700	63	0	34.61	|	—17	|	—33	24.23	|	—20	|	—32	582	1,000	—42
	4/ 3			20.2	0.710	69	0	32.53	|	—22	|	—37	23.10	|	—24	|	—35	554	980	—43
	4/ 5			19.8	0.700	70	0	34.28	41.76	—18	51.60	—34	24.00	30.35	—21	35.50	—32	576	951	—39
	4/ 7			20.0	0.710	72	0	30.84	|	—26	|	—40	21.90	|	—28	|	—38	526	1,016	—48
	4/10			20.2	0.710	68	0	39.98	|	—26	|	—40	22.00	|	—28	|	—38	528	953	—44
	4/12			20.4	0.710	72	0	31.71	|	—24	|	—38	22.52	|	—26	|	—36	541	1,002	—46
	4/14			20.4	0.710	68	0	29.40	↓	—30	↓	—43	20.87	↓	—31	↓	—41	501	981	—49
	Elevated temperature																			
	4/17			19.8	0.700	88	½	36.77	↑	—12	↑	—29	25.74	↑	—15	35.50	—27	618	1,039	—41
	4/19			19.2	0.695	90	½	43.10	|	+ 3	|	—16	29.96	|	— 1	34.40	—13	719	1,023	—30
	4/21			19.1	0.690	80	1	44.30	|	+ 6	|	—14	30.56	|	+ 1	34.40	—11	733	958	—23
	4/24			18.9	0.690	88	1	45.90	|	+10	|	—11	31.68	|	+ 4	34.40	— 8	760	870	—13
	4/26			18.5	0.680	88	1	42.00	|	0	|	—19	28.54	|	— 6	33.90	—16	685	926	—26
	4/28			17.9	0.680	88	1½	50.30	41.76	+20	51.60	— 2	34.26	30.35	+13	33.40	+ 2	822	936	—12
	5/ 1			17.9	0.678	90	1½	52.70	|	+26	|	+ 2	35.74	|	+18	33.40	+ 7	858	927	— 9
	5/ 3			17.6	0.678	100	1½	59.60	|	+43	|	+16	40.01	|	+32	32.80	+22	960	914	+ 5
	5/12			17.2	0.680	109	1½	57.40	|	+37	|	+11	38.44	|	+27	32.30	+19	923	945	— 2
	5/19			17.0	0.670	96	1½	57.35	↓	+37	↓	+11	38.43	↓	+27	32.30	+19	922	924	0
	1934																			
	1/20	6 4/12	107	17.8	0.780	88	1½	60.26	41.10	+47	50.50	+19	44.59	32.70	+36	33.40	+34	1,070	949	+13

	1936																		
	7/ 9	7 9/12	114	20.4	0.800	88	1	52.60	↑	+30	↑	+10	42.00	↑	+20	↑	+18	1,008	999	+ 1
	7/10			20.4	0.800	80	¾	43.20	|	+ 6	|	−10	34.60	|	− 1	|	− 2	830	918	−10
	7/15			20.4	0.800	80	¾	47.40	|	+17	|	− 1	37.90	|	+ 8	|	+ 7	910	960	− 5
	7/17			20.4	0.800	80	¾	49.70	|	+23	|	+ 4	39.77	|	+14	|	+12	954	996	− 4
	7/22			20.4	0.800	80	¾	41.10	40.50	+ 1	48.00	−14	32.90	34.96	− 6	35.50	− 7	790	969	−18
	7/24			20.4	0.800	80	¾	43.90	|	+ 8	|	− 8	35.20	|	+ 1	|	− 1	845	969	−13
	7/29			20.4	0.800	80	¾	46.70	|	+15	|	− 3	37.40	|	+ 7	|	+ 5	898	1,002	−10
	7/30			20.4	0.800	82	¾	47.70	↓	+18	↓	− 1	38.16	↓	+ 9	↓	+ 8	916	933	− 2
	1933																		
V.-K.	6/ 2	12	141	43.1	1.285	68	0	34.47	↑	−11	↑	−21	44.30	↑	+18	53.82	−18	1,063	1,192	− 2
	6/ 5			43.3	1.290	67	0	35.89	|	− 8	|	−17	46.31	|	+23	53.94	−14	1,111	1,050	+ 6
	6/ 7			43.8	1.300	68	0	34.31	|	−12	|	−21	44.60	|	+18	54.27	−18	1,070	1,227	−13
	6/ 9			43.9	1.300	68	0	34.19	|	−12	|	−21	44.46	|	+18	54.34	−18	1,067	1,184	−10
	6/12			44.4	1.305	68	0	32.11	|	−17	|	−26	41.90	|	+11	54.68	−23	1,006	1,245	−19
	6/14			44.8	1.310	68	0	30.33	38.80	−22	43.40	−30	39.74	37.70	+ 5	54.96	−28	954	1,123	−15
	6/21			45.6	1.330	80	0	31.13	|	−20	|	−28	41.41	|	+10	55.52	−25	994	1,209	−18
	6/23			45.9	1.330	72	1	34.88	|	−10	|	−20	46.40	|	+23	55.73	−17	1,114	1,343	−17
	6/26			46.0	1.330	84	2	35.25	|	− 9	|	−19	46.89	|	+24	55.80	−16	1,125	1,102	+ 2
	6/28			45.1	1.310	84	2	38.80	↓	0	↓	−10	50.84	↓	+34	55.17	− 8	1,220	1,154	+ 6
	1934																		
	3/ 2	12 9/12	147	46.7	1.380	96	3	53.48	38.80	+38	42.00	+27	73.80	51.74	+43	56.22	+31	1,771	1,253	+41
	1936																		
	8/ 7	15 2/12	151	56.7	1.520	80	1	41.90	39.50	+ 6	39.60	+ 5	63.70	54.68	+16	62.42	+ 2	1,529	1,587	+ 4
	1935																		
E. S.	9/10	13 4/12	96.5	18.6	0.680	84	0	33.40	↑	−14	↑	−20	22.70	↑	−23	34.00	−33	545	953	−43
	9/13			18.6	0.680	76	0	30.90	|	−20	|	−26	21.00	|	−29	34.00	−38	504	957	−47
	9/15			18.6	0.680	88	0	35.60	38.80	− 8	42.00	−15	24.22	29.65	−18	34.00	−29	581	961	−40
	12/18	13 7/12		20.0	0.705	88	0	29.22	|	−25	|	−31	20.60	|	−31	35.50	−42	494	1,046	−53
	12/27			19.1	0.690	88	1	36.82	↓	− 5	↓	−12	25.40	↓	−14	34.50	−26	610	1,057	−42
							(for 1 wk.)													
	1936																		
	1/ 4			18.1	0.680	88	2	48.10	↑	+24	↑	+15	32.70	↑	+10	33.50	− 2	785	911	−13
	1/10			16.8	0.655	80	2	53.43	|	+38	|	+27	35.00	|	+18	32.06	+ 9	840	895	− 6
	1/17			16.8	0.655	108	3	57.10	38.80	+47	42.00	+36	37.40	29.65	+26	32.06	+17	898	893	0
	1/24			16.8	0.655	100	3	53.00	↓	+37	↓	+26	34.70	↓	+17	32.06	+ 8	833	887	− 6

with true hypothyroidism, they considered this determination of greater value than that of cholesterol. They found, in addition, that the ratio of free cholesterol to total cholesterol was of no diagnostic importance in distinguishing the hypothyroid from the normal child.

Basal Metabolic Rates: The basal metabolic rates of the 3 older subjects (D. J., V. K. and E. S.) appear in detail in figure 10 and table 2; the basal energy metabolism is reported on the basis of the surface area,[30] height,[31] weight [31] and creatinine standards.[32] To compare the standards employed for interpreting the rate of basal metabolism, the original number of calories dissipated per hour by each subject is expressed on the basis of the standard indicated at the heading of each

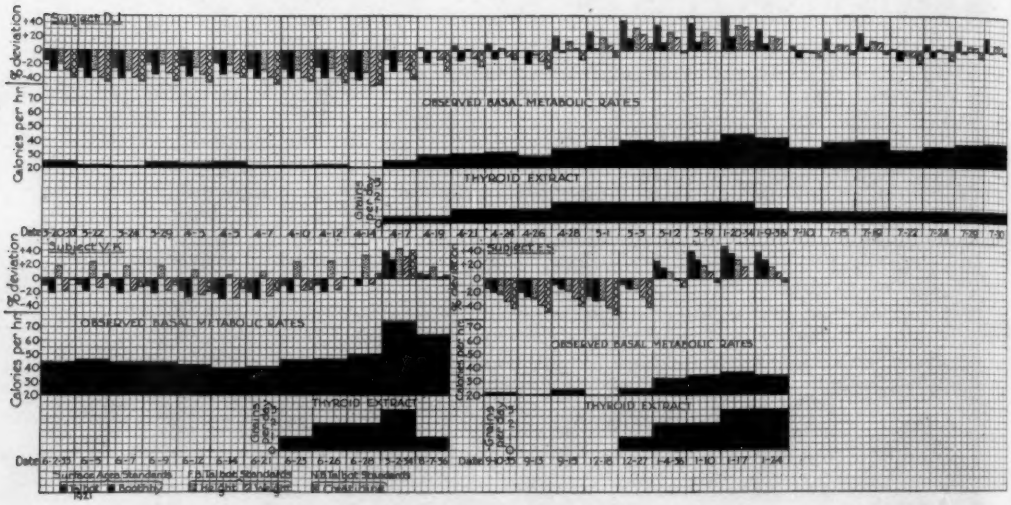

Fig. 10.—The observed metabolic rates referred to the surface area (F. B. Talbot and Boothby), height and weight (F. B. Talbot) and creatinine (N. B. Talbot) standards.

30. (*a*) Talbot, F. B.: Standards of Basal Metabolism in Normal Infants and Children, Am. J. Dis. Child. **21**:519 (June) 1921. (*b*) Boothby, W. M., and Sandiford, I.: Normal Values of Basal or Standard Metabolism: A Modification of the DuBois Standards, Am. J. Physiol. **90**:290, 1929.

31. Talbot, F. B.; Wilson, E. B., and Worcester, J.: Standards of Basal Metabolism of Girls (New Data) and Their Use in Clinical Practice, J. Pediat. **7**:655, 1935.

32. (*a*) Talbot, N. B.: Basal Energy Metabolism and Creatinine in the Urine, Am. J. Dis. Child. **52**:16 (July) 1936. (*b*) Talbot, N. B.; Stewart, A. H., and Broughton, F.: Basal Energy Metabolism and Creatinine in the Urine: II. Prediction of Basal Heat Production from Creatinine, ibid. **56**:965, 1938. (*c*) Talbot, Worcester and Stewart.[20]

column. Table 3 presents the coefficients of correlation existing between basal metabolism and urinary preformed creatinine, weight, height and surface area.

It is difficult to depend on the determination of the basal metabolic rate from any single test period for confirmatory diagnosis of hypothyroidism, because even if the child is older he usually fails to cooperate as a result of his limited mental capacity. It is necessary, therefore, to repeat the determinations often enough at sufficiently frequent intervals to get representative values.

Wilkins and Fleischmann and Block [15] found the measurement of the basal metabolic rate to be very unsatisfactory for the diagnosis of hypothyroidism. Of 33 children with unquestionable hypothyroidism, they were able to make satisfactory determinations for only 10.

Since hypothyroid children are of abnormal physical development and their chronologic age is at variance with their physiologic age, it is extremely difficult to apply normal standards based on surface area,

TABLE 3.—*Coefficients of Correlation*

	No Therapy *	Thyroid Therapy †
Basal metabolism with:		
Preformed creatinine	+0.913 ± 0.024	+0.692 ± 0.068
Weight	+0.977 ± 0.007	+0.803 ± 0.046
Height	+0.983 ± 0.005	+0.831 ± 0.040
Surface area	+0.981 ± 0.006	+0.835 ± 0.039

* Number of observations, 21.
† Number of observations, 29.

height or weight to these children. Topper and Mulier,[33] Bruch,[34] Talbot and Worcester [35] and Talbot [36] have shown the normal basal metabolic rate of obese children to be subnormal if referred to surface area and weight standards. Rowe [37] found the calculations of the deviation from the normal body surface standards to be unreliable for the rate of energy exchange in dwarfs and giants. DuBois [38] described the basal metabolism in all forms of hypothyroidism to be low but

33. Topper, A., and Mulier, H.: Basal Metabolism of Children of Abnormal Body Weight: I. Basal Metabolism of Overweight Children, J. A. M. A. **92:** 1903 (June 8) 1929.

34. Bruch, H.: Obesity in Childhood: II. Basal Metabolism and Serum Cholesterol of Obese Children, Am. J. Dis. Child. **58:**1001 (Nov.) 1939.

35. Talbot, N. B., and Worcester, J.: Basal Metabolism of Obese Children, J. Pediat. **16:**146, 1940.

36. Talbot, N. B.: Measurement of Obesity by the Creatinine Coefficient, Am. J. Dis. Child. **55:**42 (Jan.) 1938.

37. Rowe, A. W.: Endocrine Studies: XIII. The Gaseous Metabolism of Some Dwarfs and Giants, J. Nutrition **7:**573, 1934.

38. DuBois, E. F.: Basal Metabolism in Health and Disease, Philadelphia, Lea & Febiger, 1936, p. 318.

stated that the comparison with normal body surface standards often presents great difficulties.

Takahira,[39] Guhr,[40] Terroine and Lelu [41] and Terroine [42] stated the belief that a close relation exists between the excretion of creatinine and the rate of energy metabolism. Palmer, Means and Gamble [43] suggested the possibility of using urinary creatinine as a basis for evaluating basal metabolism. If the preformed creatinine excreted in the urine is the most accurate index of the amount of active protoplasmic heat-producing tissues and is independent of the total number of calories produced by the muscles, it would appear that N. B. Talbot's creatinine standard [32] would be the more closely related basis for ascertaining the basal metabolic rate of hypothyroid children.

Simulating the data of previously mentioned investigations on subjects of abnormal body proportions, the data presented in figure 10 and table 2 illustrate the difficulties encountered in applying normal standards for a given number of calories of per hour or per square meter. During the periods in which creatine is absent and no thyroid is given, one would expect all of the five basal metabolism standards used in this study to indicate a very low rate of energy exchange for a given number of calories of heat dissipated. Inspection of the protocols shows that uniform agreement frequently did not exist. Not only did we occasionally observe that for a given number of calories per hour some of the standards of reference would indicate that the rate of metabolism was low but also would we interpret it as being borderline and even within normal limits.

Considering separately each basis for interpreting the metabolic rate, it is clearly evident from the data that each standard showed an increased rate of metabolism with thyroid therapy. Even after thyroid therapy is instituted it is apparent that the same number of calories per hour or calories per square meter can at times give almost any basal metabolic rate, depending on the standard to which it is referred.

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39. Takahira, H.: Parallélisme entre l'excrétion de la créatinine et le métabolisme de base, Bull. Soc. scient. d'hyg. aliment. **15**:492, 1927.

40. Guhr, M.: Creatinine in the Urine as an Index of Degree of Basal Metabolism, West. J. Surg. **39**:921, 1931.

41. Terroine, E. F., and Lelu, P.: Le métabolisme de la crétinine et de la créatine en fonction de la grandeur de la thermogénèse, Arch. internat. de physiol. **45**:247, 1937.

42. Terroine, E. F.: Das Minimum der spezifisch-endogenen Stickstoffausscheidung. Bedingungen zur Erreichung desselben; seine Merkmale, Gründe für seine Verwendung als Basis jeder Untersuchung des Stickstoffabbaus, Biochem. Ztschr. **293**:435, 1937.

43. Palmer, W. W.; Means, J., and Gamble, J. L.: Basal Metabolism and Creatinine Elimination, J. Biol. Chem. **19**:239, 1914.

The basal metabolic rates of D. J., for instance, which Shorr [3] considered to be too high, are after treatment essentially within normal limits when referred to the creatinine [32] and the surface area standards of Boothby and Sandiford.[30b] Application of these data to F. B. Talbot's standards of 1921 [44] shows that her basal metabolic rate is too high; and according to F. B. Talbot's standards [31] for height and weight the values lie between the range of the surface area and the creatinine standards. Inspection of the protocols also reveals that as the period of therapy is lengthened the wide discrepancies (as much as 40 per cent) that exist between the results obtained with the different standards tend to disappear.

For the limited number of cases presented, N. B. Talbot's creatinine standard for evaluating the basal energy exchange did not, in general, appear to offer more accurate information than any of the other standards employed in this paper. Except in the case of V. K., the creatinine standard as well as the surface area and weight standards indicated more accurately than did the height standard the child's hypometabolism in the absence of thyroid medication. Talbot, Worcester and Stewart [20] noted that in children with thyroid diseases calculations with the weight standard in 3 cases out of 5 showed the same degree of hypometabolism as did the use of the creatinine standard.

The question arises concerning which of the body measurements, i. e., height, weight, surface area or active muscle mass (creatinine output), is the most accurate reference for the basal metabolism of the thyroid-deficient child. Although a detailed study was made on only 3 subjects, we have accumulated sufficient data on each child to apply the correlation test for finding the closest relation that existed between the basal metabolism (observed number of calories dissipated per twenty-four hours) and the four different body measurements for judging the rate of energy exchange in children. Since thyroid therapy markedly alters the dimensions of the body, the data compiled for the periods when thyroid was administered were considered apart from those for the periods when thyroid was not given.

Table 3 shows that all of the coefficients of correlation were high and positive for the periods without and with thyroid therapy. The amount of preformed creatinine, however, was not as well correlated with the energy metabolism of the three older thyroid-deficient children reported in this paper as were weight, height and surface area.

The basal metabolic rates were least correlated with the levels of urinary preformed creatinine ($+0.913 \pm 0.024$ without thyroid; $+0.692 \pm 0.068$ with thyroid) and most closely correlated with surface

44. Talbot.[30a] In a personal communication Dr. F. B. Talbot stated that his standard for surface area should be regarded as obsolete.

area ($+ 0.981 \pm 0.006$ without thyroid; $+ 0.835 \pm 0.039$ with thyroid) and height ($+ 0.983 \pm 0.005$ without thyroid; $+ 0.831 \pm 0.040$ with thyroid). The coefficients of correlation between the basal metabolic rate and the weight ($+ 0.977 \pm 0.007$ without thyroid; $+ 0.803 \pm 0.046$ with thyroid) were intermediate to the lower values for preformed creatinine and the higher values for height and surface area. On closer inspection the correlation values for weight, height and surface area appear to be essentially the same within each of the two experimental periods. The differences existing between the preformed creatinine coefficient and the coefficients of the other three basal metabolic standards (weight, height and surface area) are statistically significant when no thyroid therapy was given and statistically insignificant during the periods of thyroid therapy. Despite the inconsistency of the statistical significance of these differences, it is interesting to note that irrespective of thyroid medication the correlation values for each body measurement progressed in practically the same numerical order. The higher coefficient values in the absence of thyroid therapy appear to indicate that preformed creatinine, weight, height and surface area were more closely related to the basal metabolism of these thyroid-deficient children than when thyroid extract was administered. This suggests that in the 3 hypothyroid children receiving specific medication there were other factors that became effective in the rate of energy exchange and thereby diminished the relation that existed in the absence of thyroid therapy between the basal metabolic rate and these four body measurements.

Our data were collected from too small a number of hypothyroid children to permit us to say conclusively which body standard is best for evaluating the hypothyroid child's basal metabolic rate.

In her work with 70 children,[45] Wang [14b] found, as we did, that the basal metabolic rate was least correlated with the level of urinary preformed creatinine; however, the correlation value was high. Although she could not demonstrate any statistical differences between the coefficients of the various factors correlated with basal metabolism, she did observe that the highest correlation existed with height. Since the basal metabolic rate and the level of urinary preformed creatinine did not run parallel at all ages for the group of children Wang observed, she, too, expressed the belief that active protoplasmic tissues alone are not

45. These 70 children consisted of 24 boys between the ages of 5 weeks and 13 years and 46 girls from 4 to 15 years old. All the boys except 1, who had reached his thirteenth birthday, were under 10 years of age, and only 5 girls had reached puberty. The measurements of 55 per cent of the children were within a 10 per cent deviation from the height-weight standards of Baldwin and Wood. With the exception of 1, who was 12 per cent overweight, all were underweight, with a maximum deviation of 26 per cent. Otherwise all the children appeared normal on medical examination.

responsible for the production of either basal heat or creatinine or both, and she concluded that more work is necessary before preformed creatinine values can be safely employed as a standard for basal metabolism.

D. J. was the only subject whom we could hospitalize long enough to give us the opportunity to observe the appearance of a uniform agreement (on the rate of basal metabolism) between all the four standards. This suggests that with frequent observations on a sufficiently large number of hypothyroid children adequately treated over a long period, it may be possible to get uniform agreement from all the standards for judging their basal metabolic rates.

Up to the present investigations have not indicated the most satisfactory standard for comparing the basal metabolic rates of subjects of abnormal body proportions. Until such conclusive information is available, Lewis, Kinsman and Iliff [46] suggested that in calculating the basal metabolic rates of children whose body measurements fall outside the range of those of the children from whom standards for rate of energy exchange were established, the three standards of calories per hour per square meter referred to age, calories per hour referred to weight and calories per hour referred to body surface should be considered.

The suggestion of Shorr [3] that the creatinuria was due to abnormally high basal metabolic rates brings up the subject of the importance of the absolute values for the basal metabolic rate of an abnormally developed child. It is our opinion that the observed metabolic rate in a thyroid-deficient child is peculiar for that particular child. It is misleading to gage therapy from the resulting increased rate of metabolism alone. The administration of very small doses of thyroid will cause a sharp rise in the rate of energy exchange; on the strength of basal metabolic rate alone, it can lead one to believe that hyperthyroidism is being produced and that the dosage of thyroid should be decreased. Wilkins [47] and Means [48] stated the belief that better results can be obtained with hypothyroid children by producing a very slight degree of hyperthyroidism, being careful to avoid any toxic symptoms. The rate of energy exchange subsequent to thyroid therapy is of supplementary value only in so far as indicating that the metabolic rate of the heat-producing tissues has been augmented. Our experience has proved that the upward trend in the rate of energy metabolism from an initial low level is far more

46. Lewis, R. C.; Kinsman, G. M., and Iliff, A.: The Basal Metabolism of Normal Boys and Girls from Two to Twelve Years Old, Inclusive, Am. J. Dis. Child. **53**:348 (Jan., pt. 2) 1937.

47. Wilkins, L.: Thyroid Medication During Childhood, J. A. M. A. **114**:2382 (June 15) 1940.

48. Means, J. H.: Hypothyroidism: Diagnosis and Treatment, Bull. New York Acad. Med. **16**:14, 1940.

significant in the cases of hypothyroid children than the establishment of actual numerical values (i. e., ± 15 per cent). It has been our practice to rely on changes in basal energy rates only in subordination to the clinical, physical, mental and osseous progress when gaging the dosage of thyroid.

Hypothyroid Infants: The values for urinary creatine and creatinine excretion of 3 hypothyroid infants, B. C., E. L. and G. E., appear in table 1. Several comprehensive studies [49] have established the presence of creatine in the urine of normal infants. The two conditions besides hypothyroidism in which creatinuria is diminished or absent are prematurity [49c] and myotonia congenita,[50] which, with the possible exception of the latter, should not present difficulties in differential diagnosis.

In the absence of thyroid therapy 2 of the 3 hypothyroid infants reported on in this study excreted negligible amounts of creatine (B. C., average daily value 1 mg.; E. L., average daily value 2 mg.), whereas the third child showed a very low average level (G. E., 14 mg. per twenty-four hours). Inspection of the data reveals a definite increase in urinary creatine, which gradually approached the levels for normal infants as a result of continuous thyroid therapy. The range of the average increased values with thyroid therapy were from 22 to 116 mg. (B. C.), 64 mg. (E. L.) and 86 to 132 mg. (G. E.). Clinical improvement followed the establishment of a normal type of creatine excretion in these infants. These observations are compatible with the conclusions drawn by Catherwood and Stearns [49a] from their work on normal infants. They stated the belief that it is an increase in activity of endogenous (thyroid) factors and not age, weight nor muscle mass (creatinine) that is responsible for the increase in rate of energy exchange in combination with the increased output of urinary creatine that occurs in the growing infant.

The experimental periods for subjects B. C. and E. L. were too short to show any significant influence of thyroid therapy on the absolute levels of creatinine excreted in the urine. The amounts of creatinine excreted by G. E. remained unaltered for thirteen weeks after therapy with thyroid was instituted, even though her body weight was steadily increasing. For G. E. the period of thyroid therapy was of sufficient

49. (*a*) Catherwood, R., and Stearns, G.: Creatine and Creatinine Excretion in Infancy, J. Biol. Chem. **119**:201, 1937. (*b*) Daniels, A. L., and Hejinian, L. M.: Growth of Infants from the Standpoint of Physical Measurements and of Nitrogen Metabolism: II. Creatine, Am. J. Dis. Child. **38**:499 (Sept.) 1929. (*c*) Marples, E., and Levine, S. Z.: Creatinuria of Infancy and Childhood: I. Normal Variations; Creatine Tolerance Tests and the Effects of Amino-Acetic Acid in Normal Infants, ibid. **51**:30 (Jan.) 1936.

50. Poncher, H. G., and Woodward, H.: Pathogenesis and Treatment of Myotonia Congenita, Am. J. Dis. Child. **52**:1065 (Nov.) 1936.

duration to show the diminishing effects of thyroid medication on preformed creatinine. It is possible, however, that her continuous gain in weight (muscle mass), resulting from adequate therapy, prevented her from exhibiting a decreased level of urinary creatinine.

The cholesterol values were of no diagnostic value (values ranged from 167 to 278 mg. per hundred cubic centimeters). The roentgenogram for B. C. and G. E. indicated normal ossification of the carpal centers, since they had apparently received treatment sufficient to bring about normality of osseous development before therapy was discontinued. The subjects were too young to have their basal metabolic rates determined with the facilities of this hospital, as we do not have a closed respiratory chamber.

COMMENTS

The diagnosis of hypothyroidism in infants presents some difficulties, particularly in determining basal metabolic rates, for few institutions are equipped to perform such studies on babies. Furthermore, basal metabolism as ordinarily determined in young and in hypothyroid children is unreliable and offers great difficulties in comparison with normal standards. Although the number of hypothyroid subjects presented in this investigation is small, the results have indicated that blood cholesterol values and roentgenograms are not always informative. Only 2 subjects of the total 6 exhibited elevated levels of cholesterol; and because of previous therapy only 2 exhibited any delay in the appearance of the carpal centers at the wrist. This led to our seeking additional diagnostic and therapeutic aids for infants and children with borderline conditions. The absence or diminution of physiologic creatinuria in untreated hypothyroid children has been established. We have used and discussed the application of this criterion in supporting a diagnosis of hypothyroidism in children.

In the investigations reported by Wilkins, Fleischmann and Block [15] they concluded that there is a tendency for the creatine excretion to be low in hypothyroid children, but many normal children may have a creatinuria of the same magnitude as that of untreated cretins. This conclusion is at variance with the statements in the literature concerning the contrast between the excretion of creatine by normal and by hypothyroid children. Perhaps this discrepancy may be explained by the type of control subjects selected by Wilkins and his collaborators. They used 26 children of normal height and weight, of whom 18 had old quiescent orthopedic conditions. They stated that 9 of these patients had muscular atrophy from disuse because they were immobilized in casts, and consequently the creatine level in their urine was abnormally high. Therefore, Wilkins and his associates could not consider these subjects as true normal controls, and they were so designated on the charts. On

the other hand, one also questions the normalcy of the other 9 orthopedic subjects who were immobilized in casts, and one must consider the effect of muscular activity on the levels of creatine excreted in the urine.

It has been reported [51] that in normal adult males a close relation exists between creatinuria and muscular activity. Although the urinary creatine of men occurs in very small amounts and may even be absent, Hobson [51c] observed that adult male physical education students excreted from 92 to 1,200 mg. of creatine per twenty-four hours. He found that muscular exercise did have some influence on the high creatinurias of these men. Two groups of investigators [52] observed that when their normal adult male subjects were confined to complete rest in bed the amounts of creatine they eliminated were considerably less than when they were engaged in the usual physical activities of their daily routine work. If the orthopedic patients accepted by Wilkins and his associates in their normal control group were entirely free from muscular atrophy, one would suspect that their restricted muscular activity would cause a lowered creatine output.

The difficulty in securing physically and physiologically normal children whose activities have not been restricted is well appreciated. Since the range of creatine excreted by normal children has not been definitely established and all of the factors influencing the excretion of creatine have not been fully determined, we believe that the use of orthopedic patients as normal controls is open to question.

Dr. Genevieve Stearns has given us access to valuable unpublished information from adequately controlled and continued experiments concerning the creatine and creatinine metabolism of normal run-about children. Dr. Stearns stated that she has never seen a normal child who did not excrete creatine. She has had subjects who sometimes excreted no creatine one day and several hundred milligrams the following day. In a few of her normal subjects whose three to five day average excretion of creatine fell below 50 mg. per day, the low value in each case was preceded and/or succeeded by a much larger value.

In their distribution graph (figure 4, page 9), Wilkins, Fleischmann and Block [15] gave the following information concerning the absolute amounts of creatine excreted by their normal and by their hypothyroid subjects: Over experimental periods of seven to fourteen days all of their 13 cretins excreted less than 90 mg. per day; 12 of these 13 cretins excreted less than 50 mg. per day. Six of the 17 control children, free

51. (*a*) Light, A. B., and Warren, C. R.: Creatinuria Among Adolescent Males, J. Biol. Chem. **104**:121, 1934. (*b*) Taylor, F. H. L., and Chew, W. B.: Creatinuria in Adult Males, Am. J. M. Sc. **191**:256, 1936. (*c*) Hobson, W.: Urinary Output of Creatine and Creatinine Associated with Physical Exercise and Its Relationship to Carbohydrate Metabolism, Biochem. J. **33**:1425, 1939.

52. Light and Warren.[51a] Taylor and Chew.[51b]

from any detectable muscular dystrophies, excreted less than 90 mg. of creatine per day. Of these 6, only 2 excreted less than 50 mg. per day. Bearing in mind the type of subjects used as controls, we feel that Wilkins and his co-workers have attached too much significance to the overlapping of their creatine values in their groups of control and hypothyroid children.

In an attempt to distinguish between the biochemical processes of the hypothyroid and of the normal child, Wilkins, Fleischmann and Block [4] measured the increase in creatine output and the decrease in serum cholesterol in response to thyroid. Their actual observations [53] showed, and they stated, that the per cent rise in urinary creatine above the base level demonstrated a far greater distinction between their hypothyroid and control groups than did the decrease in serum cholesterol.

For daily doses of ¼, ½ and 2 grains (0.015, 0.03 and 0.13 Gm.) of thyroid, the respective increases in creatine output above the base levels of the hypothyroid children were: 60 to 1,600 per cent, 138 to 2,750 per cent and 248 to 6,250 per cent. For these same dosages of thyroid in the control group, the respective increases in creatine output above the base levels were: 0, 0 to 55 per cent and 0 to 164 per cent. Wilkins and his collaborators could not demonstrate any great differences between the hypothyroid and control groups on the basis of the range in the creatine output in response to the previously mentioned doses of thyroid. They stated, however, that if the creatinuria response to thyroid medication was measured by the percentage increase of creatinuria above the base levels, marked differences between the hypothyroid children and their control cases were apparent.

Serum cholesterol decreased markedly with as little as ¼ grain of thyroid daily in some of the hypothyroid children. With ½ grain of thyroid daily the reduction in serum cholesterol in the hypothyroid group ranged from 78 to 305 mg. per hundred cubic centimeters, or 33 to 57 per cent below the control level, and with 2 grains the reduction ranged from 120 to 385 mg. per hundred cubic centimeters, or 44 to 63 per cent below the base level. In the control groups only 2 grain doses of thyroid were given and the maximum decrease was 77 mg. per hundred cubic centimeters, which represented a maximum decrease of 28 per cent below the control level.

This same group of investigators selected the effect of a single dose of thyroxin on the serum cholesterol in preference to creatinuria in further investigating a means of differentiating between hypothyroid and normal children. They stated that they found creatinuria was the earliest and most sensitive indication of thyroid effect in children. They concluded, however, that the study of the response to the daily oral

53. Wilkins, Fleischmann and Block,[4] table 2, p. 17.

administration of thyroid or to the injection of a single dose of thyroxin showed that the effect on the serum cholesterol serves better to differentiate the hypothyroid from the normal child than does the change in creatinuria.

Because there is no one chemical test which is a measure of thyroid activity alone, we do not feel that one can justifiably state that for all hypothyroid children one chemical test is preferable. We do concede that it is more convenient to carry out studies of serum cholesterol than it is to conduct investigations of urinary creatine, but from our experience cholesterol determinations are by no means more informative in cases of hypothyroidism than carefully controlled creatine studies.

We have shown that determination of the level of creatinuria in 6 hypothyroid children was a valuable aid in the diagnosis. In an earlier report, we expressed the opinion that the amount of creatine excreted by thyroid-deficient children might be used in gaging the effect of thyroid medication. With further experience we feel that the value of the level of urinary creatine is limited and serves only as an adjunct to the structural and functional observations on which the diagnosis of hypothyroidism is based. So far as we know, there are no biochemical or metabolic tests which by themselves are unequivocal in establishing the diagnosis of hypothyroidism or in regulating the dosage of thyroid.

SUMMARY AND CONCLUSIONS

The creatinuria produced in 4 hypothyroid children by thyroid therapy was continuous with continuous therapy. It is most logically explained on the basis of the establishment of the physiologic creatinuria of childhood.

The establishment of a normal type of creatine metabolism was followed by clinical improvement in the 6 subjects reported.

Determinations of the urinary output of creatine may serve as a valuable aid in the diagnosis of hypothyroidism, especially in infants and in older children when initial cholesterol levels are within normal limits and the osseous development has progressed to normal. At present, however, biochemical and metabolic tests are not sufficient in themselves for the diagnosis of hypothyroidism or for the regulation of dosage of thyroid.

Basal metabolic rates in 3 hypothyroid children varied widely depending on the standard of reference used. We consider the upward trend in the basal metabolic rate as affected by therapy far more significant than the actual numerical values. The rate of energy exchange observed in the thyroid-deficient children was not as closely related to the urinary preformed creatinine as it was to height, weight and surface area.

Statistical analyses were made and interpreted by Dr. Mildred A. Norval.

NONOBSTRUCTIVE HYDROCEPHALUS

TREATMENT BY ENDOSCOPIC CAUTERIZATION OF THE CHOROID PLEXUSES

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A sound rationale for the treatment of nonobstructive (communicating) hydrocephalus by extirpation of the choroid plexuses from the cerebral ventricles was first advanced by Dandy [1] in 1918.

The original operative technic proposed by Dandy to accomplish this end was essentially an "open" operation, in the sense that the cerebrospinal fluid was first evacuated from the two lateral ventricles, after which surgical extirpation of the two choroid plexuses was performed in a dry field under direct vision (fig. 2 *A*). This procedure was simple and direct, but Dandy [1] stated that in cases of hydrocephalus of certain degree . . . "death will follow almost immediately upon the release of fluid. . . . In the advanced cases we can hold out very little encouragement from operative procedures of any kind which will necessitate release of fluid and collapse of the brain. In three [of four] cases of this series . . . there was an immediate operative collapse beginning with pallor of the face and body, rapid feeble pulse which quickly became imperceptible, cold clammy perspiration, rapid shallow and irregular respiration. . . . These things invariably began with evacuation of ventricular fluid. . . . Following escape of the fluid the thin brain walls collapse. . . . The mechanical kinking of the larger vascular trunks by angulation of the infolding brain must have a pronounced effect upon the circulation."

Unfortunately, no statistics are available regarding the operative mortality accompanying Dandy's operation. In his original article (1918) this author reported that he had operated on 4 children, of whom only 1 had survived longer than three weeks. In an article written for Lewis' "Practice of Surgery" [2] fourteen years later (1932)

Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Atlantic City, N. J., June 9, 1941.

From the Department of Neurology, Columbia University College of Physicians and Surgeons, and the Division of Neuro-Surgery, Neurological Institute of New York.

1. Dandy, W. E.: Extirpation of the Choroid Plexus, Ann. Surg. **68**:569 (Dec.) 1918.

2. Dandy, W. E.: Hydrocephalus, in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, p. 213.

Dandy again described his original operative technic but reported no new cases or any statistics covering his results. A careful review of the literature, furthermore, has failed to yield any reports on children with nonobstructive hydrocephalus successfully treated by other surgeons employing Dandy's methods during the sixteen years from 1918 to 1934.

The results of the treatment of hydrocephalus by the older method were thus most discouraging, when, in 1934, Putnam [3] published his important paper describing the endoscopic cauterization of the choroid plexuses. The fundamental principle was the same as that advanced by Dandy, namely, reduction of the secretion of cerebrospinal fluid by destruction of parts of the choroid plexuses. But Putnam's adaptation of the endoscope, in the form of a new "ventriculoscope," to this problem obviated the necessity, inherent in Dandy's original technic, of evacuating the cerebrospinal fluid from the ventricular cavities. Thus his procedure prevented collapse of the ventricular walls and greatly reduced the operative shock which had attended the earlier type of operation and had resulted in such a prohibitive operative mortality.

In his original report Putnam described 12 operations performed on 7 children, with only 2 deaths, which possibly were not directly attributable to the operation itself. His report marks a turning point in the treatment of this condition. In a subsequent communication [4] Putnam described 49 operations performed on 26 children, with 10 deaths, a mortality of only 21 per cent from the 49 operations. In the last 11 cases, moreover, there had been but 2 deaths from 16 operations, so that the case mortality was only 18 per cent and the operative mortality only 12 per cent for this selected group. Seven of the 26 children were still alive at the time the report was made (1938), and 5 of these, aged 3 years, 2¾ years, 1½ years, 1 year and 1 month respectively, were thought at that time to have normal mentality for their ages. In a personal communication just received Putnam reported that in his "new series" (1935 to 1940) 16 children were operated on 21 times, with 4 hospital deaths. Five patients, however, are still living five to seven years after operation.

In January 1934, using an ordinary operating cystoscope, I cauterized the choroid plexus, first on one side and later on the other, in 1 patient (case 1, group 3). When Putnam's original article appeared in June 1934 I was working on a specialized endoscope for use within the cerebral ventricles. In October 1934 I first reported [5] on this "ventricu-

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3. Putnam, T. J.: Treatment of Hydrocephalus by Endoscopic Coagulation of the Choroid Plexus: Description of a New Instrument and Preliminary Report of Results, New England J. Med. **210**:1373 (June 28) 1934.

4. Putnam, T. J.: Mentality of Infants Relieved of Hydrocephalus by Coagulation of Choroid Plexuses, Am. J. Dis. Child. **55**:990 (May) 1938.

5. Scarff, J. E.: On the Treatment of Hydrocephalus, J. Pediat. **6**:870 (June) 1935.

loscope," at the meeting of the American Academy of Pediatrics and gave data from 1 case in which operation was performed. In June 1935, at the annual meeting of the American Neurological Association, I described [6] this instrument and the technic of its use more fully (figs. 1 and 2); I also made a preliminary report on 9 operations performed on 5 patients, with encouraging results. In 1938 [7] I discussed this subject in considerable detail and presented a general review of the broader aspects of hydrocephalus in childhood, including considerations of etiology, diagnostic measures, selection of methods for treatment and operative technic. The reader is referred to that report.

The present paper is a report of my personal experiences and a summary of the results I have obtained in the treatment of communicating hydrocephalus by endoscopic cauterization of the choroid plexus during the past seven years.

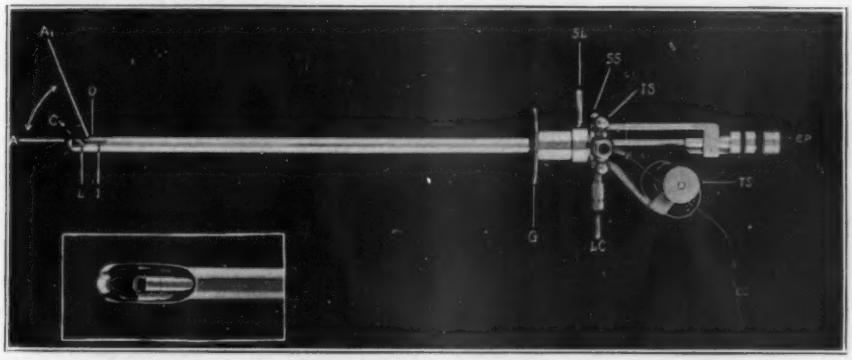

Fig. 1.—The author's "ventriculoscope" which I designed. A special lens system permits both forward and lateral vision, as indicated by the lines *OA* and *OA* 1. The cautery tip (*C*) can be advanced or retracted as desired by means of the thumb screw (*TS*). Irrigation of the operative field is controlled by a stopcock (*IS*). *LC* is the lighting connection leading to the battery box; *EC* is the connection between the cautery and the endothermy machine.

METHODS AND MATERIAL

In all of the operations here reported I used the instrument and the technic previously described (figs. 1 and 2).

The operative procedure, which has become more or less standardized, may be described as follows. Anesthesia induced by avertin with amylene hydrate in combination with local infiltration is used. The patient is placed face downward, with the face in a cerebellar head rest. Trephine openings about 1 inch (2.5 cm.) in diameter are made over the occipital lobes, slightly more lateral and superior

6. Scarff, J. E.: Endoscopic Treatment of Hydrocephalus: Description of a Ventriculoscope and Preliminary Report of Cases, Arch. Neurol. & Psychiat. **35:** 853 (April) 1936.

7. Scarff, J. E.: Neurosurgical Diseases of Childhood: Hydrocephalus, in Brenner, E. C.: Pediatric Surgery, Philadelphia, Lea & Febiger, 1938.

to the site usually selected for trephination for ventriculographic examination. At present both sides are usually operated on at the same session. Interrupted black silk sutures are usually placed in the galea and then retracted out of the field before the dura is opened. Closure is thus greatly facilitated.

Attention is directed to the reservoir and the irrigating system by which the intraventricular pressure is maintained at a nearly constant level throughout the operative procedure (fig. 2). This prevents the collapse of the ventricular wall away from the cranial vault which contributed so greatly to the shock experienced by the patients operated on by Dandy.[8]

Ringer's solution may be used as an irrigating fluid during the cauterization but I prefer to use the special buffered Ringer's solution ("artificial spinal fluid")

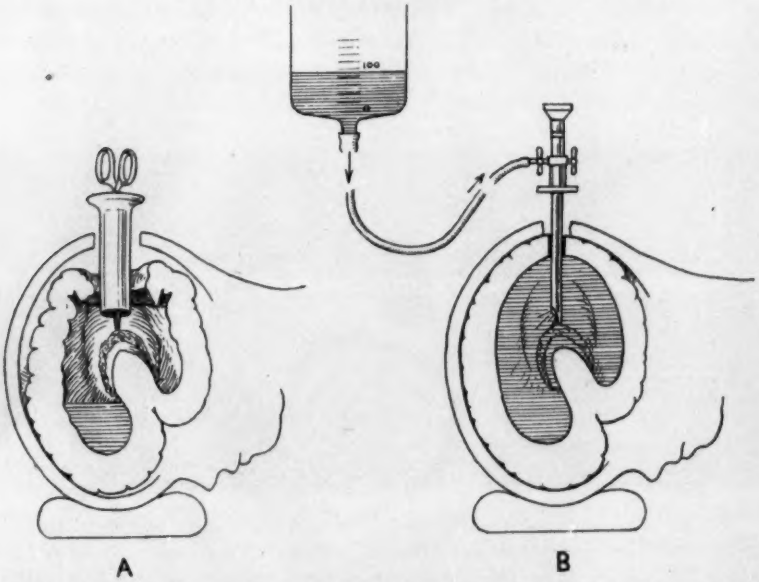

Fig. 2.—The treatment of nonobstructive (communicating) hydrocephalus requires destruction of the choroid plexuses, which produce the excess of cerebrospinal fluid. Dandy's original technic (*A*) accomplished this but required evacuation of the fluid from the ventricles preceding the surgical excision of the plexuses. This resulted in collapse of the ventricular walls, with attendant shock and an elevated operative mortality (see text).

The endoscopic cauterization of the choroid plexus does not require evacuation of the ventricular fluid, and my technic (*B*) further provides for a constant fluid pressure within the ventricles during the operation by means of a reservoir of irrigating fluid. This prevents collapse of the walls of the ventricles and minimizes operative shock.

The operative mortality as a result of this improved technic has been reduced to less than 15 per cent. For protocols of the cases in which death resulted from operation, see text ("group 1").

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8. In a discussion of this paper, which was read at the annual meeting of the American Neurological Association at Atlantic City on June 9, 1941, Dandy

of Sachs. The basis for this preference will be given elsewhere in the section of this paper devoted to a discussion of results.

At the time of injection into the ventricles this buffered solution closely resembles normal cerebrospinal fluid as far as the content of sodium, potassium, calcium, magnesium, chloride and bicarbonate and p_H is concerned. Because of its bicarbonate content the solution has to be prepared in two parts, which, after sterilization by autoclaving and proper dilution, are mixed in equal amounts just before using.

According to information supplied by Dr. A. F. Hartmann, of the department of pediatrics, the "artificial spinal fluid" is prepared as follows:

Solution 1 (Concentrated):

Sodium chloride	300 Gm.
Potassium chloride	19 Gm.
Calcium chloride	10 Gm.
Magnesium chloride	20 Gm.
Add distilled water to make 1 liter	(1,000 cc.)

Filter the solution (preferably through a glass disk filter to exclude filter paper fibers). Autoclave at 15 pounds' (6.8 Kg.) pressure for thirty minutes. This concentrated solution 1 should keep in pyrex glass indefinitely.

To prepare for mixing with solution 2, measure accurately 10 cc. (with a sterile pipet, so as not to contaminate the stock solution) and make up to 250 cc. with freshly distilled water. (It is convenient to do this in a 250 cc. volumetric flask. Make up to the mark and then withdraw 10 cc. with the same pipet, leaving 240 cc.) Place this amount in a pyrex glass flask or bottle of 500 cc. capacity, mix and resterilize by autoclaving at 15 pounds for thirty minutes. Stopper with a sterile (autoclaved) cork or rubber stopper. It is usually convenient to prepare about six such bottles of 240 cc. each of solution 1. This solution may be resterilized at any time, if it is thought advisable.

Solution 2:

To exactly 5 Gm. of anhydrous sodium carbonate add a few milligrams of dry phenol red (phenolsulfonphthalein) and make up to 1 liter (1,000 cc.) with freshly distilled water. Filter free of any suspended particles. Measure 240 cc. into a pyrex glass flask or bottle of 500 cc. capacity and sterilize by autoclaving at 15 pounds for thirty minutes. Stopper with a sterilized (autoclaved) cork. In this condition the solution may be resterilized at any time if it is thought advisable.

Just before using add exactly 1 cc. (measured with an accurate sterile pipet) of concentrated hydrochloric acid (36 per cent) to 240 cc. of solution 2 and mix by rotating the flask or bottle. The sodium carbonate should now be converted into sodium bicarbonate plus sodium chloride, and the color should change from red to an orange shade. (If such a change does not occur a drop more of the acid should be added.) At this stage the solution can no longer be resterilized.

Pour equal parts of solution 2 (after the addition of the hydrochloric acid) into solution 1 and mix by rotating the flask. This final mixture has the composition of normal spinal fluid and is ready for injection into the ventricles.

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stated that he now places plaster casts about the outside of the child's head preoperatively and claimed that this procedure is completely effective in preventing collapse of the thinned-out cortex away from the inside of the skull after he has emptied out the cerebrospinal fluid from the ventricles.

The patients here reported on include all of the patients with nonobstructive hydrocephalus whom I treated at New York Post-Graduate Medical School and Hospital prior to March 1937 and at the Neurological Institute of New York after that date.

Forty-eight operations have been performed on 20 children; an operation within either of the lateral ventricles has been regarded as one operation, and operations within both lateral ventricles have been regarded as two operations, regardless of whether the operations were performed at different times or at the same time.

For presentation and discussion the cases have been arranged into three groups on the basis of the end results: Group 1 consists of the 3 cases in which death resulted from the operation. Group 2 includes 7 cases in which the child survived operation but the end result must be regarded as unfavorable. Group 3 embraces

TABLE 1.—*Data for the Three Cases in Group 1, in Which Death Resulted from the Operation* *

Case No.	Patient	Date of Operation	Side Operated on	Postoperative Course
1	A. R.	5/27/35	Right	Operation satisfactory and uncomplicated; immediate postoperative status good; 7 hours after operation transient, slight, generalized twitchings of all the extremities; 12 hours after operation, onset of generalized tonic and clonic convulsions, hyperthermia and death
2	J. W.	5/ 5/37	Right	Operation satisfactory and uncomplicated; immediate postoperative status good; 3 hours after operation, onset of intermittent, spastic states affecting both sides of the body; temporary improvement; 6 hours after operation sudden opisthotonos and respiratory failure
3	F. F.	4/ 6/35	Right	Immediate postoperative status good, but cardiac decompensation and pulmonary edema appeared due to blood transfusion which was too large and too rapidly given; death not truly attributable to the operation itself

* In the 3 cases in group 1 which comprise 15 per cent of the entire series, 3 operations were performed.

the 10 cases in which the child survived operation and the end result may be regarded as favorable.

For those interested in the technical problems related to the treatment of hydrocephalus individual protocols have been reported in sufficient detail to include all pertinet data. For those interested only in the more general aspects of the problem the salient facts have been abstracted and condensed into tabular form (tables 1, 2 and 3).

REPORT OF CASES

GROUP 1: THREE CASES IN WHICH DEATH RESULTED FROM OPERATION

CASE 1.—A. R., a 7 month old, typically hydrocephalic boy, was admitted to the Post-Graduate Medical School and Hospital on May 24, 1935. The maximum circumference of the head was 20½ inches (52 cm.). The results of the dye test indicated that he had nonobstructive hydrocephalus.

Operation.—On May 27, with the patient under ether anesthesia, cauterization of the choroid plexus of the right lateral ventricle was carried out. There were

no complications. The entire operation required sixty minutes. The patient's condition was good at the end of the procedure.

Postoperative Course.—The patient was returned to the ward at 12:30 p. m. in good condition. The skin was warm, dry and pink. The temperature and the pulse and respiratory rates were normal.

At 7 p. m. there was observed a slight, transient spastic state, accompanied by fine generalized tremors which lasted one or two minutes. About midnight the fine tremors reappeared, together with an intermittent spastic state involving the body and all four extremities but no clonus. At this time the fontanel was flat and soft. The child was alert. He took water and milk avidly. After five or ten minutes the tremors and the spastic state disappeared, and the child then looked well and was alert.

At 3:30 a. m. convulsions began again. At their onset the child was responsive and alert. The fontanel was slightly depressed; the temperature was 101.5 F. (per rectum); the pulse was of good quality and the rate was 150 per minute; the respiratory rate was 22. The skin was of good color, dry and warm. Intermittent spastic states then developed; they gave place rapidly to clonic spasms involving all of the extremities, which became continuous until true status epilepticus ensued. The child became cyanotic; the blood vessels of the scalp collapsed, and the fontanel became acutely depressed. Physiologic solution of sodium chloride was quickly introduced into the ventricle by needle in an effort to equalize the intracranial and extracranial pressures. But in spite of this the child died within the space of a few minutes.

Autopsy.—Death appeared to be due solely to the operation, although the mechanism was not clear. Autopsy revealed nonobstructive hydrocephalus but nothing else which shed any light on the origin of the convulsions or the cause of death.

It is noteworthy that the first transient signs of impending trouble did not appear until seven hours after the operation and did not reappear until five hours later. Also, it should be observed that these signs were bilateral and generalized despite the fact that operation had been performed only on the right side of the brain. The significance of these facts will be discussed later in connection with the similar results in case 2 of this group.

Attention is also directed to the acute intraventricular hypotension which was encountered as a postoperative complication for the first time in this case. It undoubtedly contributed in some part to the infant's death. This phenomenon was seen in 2 subsequent cases, in both of which, however, the patient survived (cases 2 and 9, group 3).

Case 2.—J. W., a 6 week old boy, was admitted to the Neurological Institute on April 28, 1937 with acute hydrocephalus. The head measured 17¼ inches (44 cm.) in diameter. The results of the dye test indicated that he had a communicating type of hydrocephalus. His general condition was good, and he appeared to be a good operative risk.

Operation.—Cauterization of the right choroid plexus was performed on May 5, with the patient under anesthesia induced by avertin with amylene hydrate supplemented with ether. The procedure was carried out in the usual manner, without

any complications. Throughout the operation there was maintained constant irrigation of the ventricular cavity with Ringer's solution. The choroid was easily found and thoroughly cauterized. During the procedure there was no change in the patient's condition, and he left the operating room at 10:30 a. m., apparently in excellent condition.

Postoperative Course.—At noon the temperature was 101 F., the pulse rate 160 and the respiratory rate 48. He was pink and beginning to come out of the anesthesia. He cried lustily and moved all of his extremities.

At about 1:30 the baby began to have transient, intermittent, tonic seizures, in which all of the extremities would stiffen out and even the back was sharply arched in the position of opisthotonos. The abdomen became distended, and the abdominal muscles at first became spastic and subsequently underwent curious rhythmic contractions, suggestive of the powerful peristaltic movement associated with acute intestinal obstruction. The temperature at this time was 106.8 F. After about one hour, however, the muscular spasm of the extremities, back and abdomen ceased. The baby seemed much better. The temperature gradually fell; at 6:30 p. m. it was only 102.5 F. At this time he took all of his regular formula avidly.

At 6:50 p. m., however, he cried out shrilly and suddenly ceased breathing. A few moments later his heart stopped beating. It was noted that his body and extremities suddenly had again become rigid. Permission for autopsy, unfortunately, was not obtained.

Death was undoubtedly the result of the operation, but the mechanism was obscure. It is noteworthy that almost three hours had elapsed after the operation before the appearance of the spastic and clonic states, which were bilateral.

These phenomena closely resemble those which occurred in case 1 of this group and suggest that a similar mechanism was involved. This point will be considered later, in the discussion of the cases of this group.

CASE 3.—F. F., a 4 month old hydrocephalic boy, was admitted to the Post-Graduate Medical School and Hospital on April 6, 1935. His head had begun to enlarge abnormally about two months previously. At the time of admission its maximum circumference was 20½ inches (52 cm.). The results of the dye test indicated that he had a communicating type of hydrocephalus.

Operation.—On April 16 the right choroid plexus was cauterized, with the patient under ether anesthesia. Some slight bleeding from the plexus occurred at one point, but irrigation quickly cleared the visual and operative fields, and the procedure was completed without difficulty. It was estimated that not more than 5 or 10 cc. of blood was lost before the bleeding stopped.

Postoperative Course.—At the end of the operation the patient's condition was, on the whole, good, but since the father had been brought to the operating room floor and prepared to give blood it was thought just as well to give the child a transfusion. Unfortunately, this was done too rapidly. While the patient was still receiving the blood his condition abruptly changed. The pulse became rapid and feeble, the respirations became gasping, the skin turned blue, gurgling sounds were heard over the chest and there was frothing at the mouth. The transfusion was instantly stopped and general supportive measures employed, but the child died.

Clinically, death appeared to be due to acute decompensation of the right side of the heart with pulmonary edema, due to an ill advised

and too rapidly given transfusion. Although the outcome was classified as an operative death for statistical purposes, I feel that the fatality in this instance was not truly attributable to the operative procedure itself.

GROUP 2: SEVEN CASES IN WHICH THE PATIENT SURVIVED OPERATION BUT THE END RESULT WAS UNFAVORABLE

CASE 1.—J. B., an 8 month old boy, was admitted to the Neurological Institute on May 9, 1938. He looked sturdy but had the characteristic stigmas of hydrocephalus. The posterior fontanel was widely open and bulging. The maximum circumference of the head was 29⅝ inches (62.5 cm.). The patient's general physical status was good and the prospect of a favorable outcome seemed unusually promising.

Operations.—With the patient under anesthesia induced by avertin with amylene hydrate, attempts to cauterize the right and the left choroid plexus were made on several occasions. In each instance, however, the procedure had to be terminated almost as soon as cauterization was started because of technical difficulties with the electrical equipment. These were eventually corrected, but during the delay which they had occasioned the child's head had grown to such proportions that further surgical procedures seemed clearly contraindicated. He was discharged, therefore, to a hospital for chronic diseases, unimproved (fig. 3).

This was one of the most unsatisfactory and disappointing of the series of cases, but failure in this instance was due entirely to technical and instrumental difficulties and not to any fault of the surgical procedure.

CASE 2.—C. O., a 5 month old boy, was admitted to the Neurological Institute on July 5, 1938 because of slow, gradual enlargement of the head. On admission its maximum circumference was 22 inches (56 cm.). The results of the dye test indicated that the child had a communicating type of hydrocephalus.

Operations.—On July 15, with the patient under anesthesia induced by avertin with amylene hydrate, cauterization of the right choroid plexus was satisfactorily performed. On August 26 a similar procedure was carried out on the left side. The child tolerated both operations extremely well.

Postoperative Course.—The intracranial pressure was greatly reduced for several weeks (fig. 3). But soon thereafter it increased, and the child was finally discharged to a sanatorium on November 22, almost three months after the second operation, unimproved.

The last report concerning this patient was received from the physician in charge of the sanatorium on March 15, 1941. At that time, according to the letter, the child was in good general physical condition. His head then measured 26 inches (65 cm.) in diameter, an increase of 3½ inches (9 cm.) over its diameter at the time of discharge. It was said that he was alert, could sit up and was interested in his surroundings.

Obviously, the result in this case is "unsatisfactory," in that the intracranial tension was never permanently reduced to a normal level by the operation. In retrospect, I feel that the failure in this case might

TABLE 2.—*Data for the Seven Cases in Group 2, in Which the Patient Survived Operation but the End Result Was Unfavorable* *

Case No.	Patient	Date of Operation	Side Operated On	Postoperative Status	Date of Discharge	Status on Discharge	Subsequent Course
1	J. B.	6/ 2/38 6/16/38	Right Left	Unsatisfactory operation; slight temporary improvement; rapid return of pressure	7/16/38	Fontanel tense; head enlarging; pressure not relieved	Lived 3 months; died at home; no details available
2	C. O.	7/13/38 8/26/38	Right Left	Temporary improvement; gradual return of pressure	11/22/38	Fontanel full and soft temporarily; pressure not relieved permanently	Alive 3/3/41; head still enlarging; mentally dull
3	L. P.	9/19/40 9/19/40 10/18/40 10/18/40	Right Left Right Left	Temporary improvement after first operations; early return of pressure; no reduction of pressure after second operation	11/ 7/40	Fontanel full; head slightly enlarged; pressure not relieved permanently	Alive 3/15/41; fontanel full but not tense; head slowly enlarging; mentally bright
4	R. M.	6/30/37 11/ 8/37	Right Left	Unexplained postoperative fever; pressure reduced	12/31/37	All decompression areas soft and depressed; pressure relieved	Died 2/7/38 at home, of unexplained acute febrile illness; decompression areas all depressed
5	J. C.	8/11/37 11/13/37	Right Left	Satisfactory; fontanel depressed	11/29/37	Fontanel depressed and smaller; bones overriding; head smaller; pressure relieved	Died 12/16/39 at Montefiore Hospital, of acute bronchopneumonia
6	I. M.	12/30/37	Right	Satisfactory; fontanel markedly depressed	1/23/38	Fontanel markedly depressed; bones of skull overriding; head smaller; pressure greatly reduced	Died 4/10/38 at home; no details available
7	H. F.	11/14/40 11/14/40 12/30/40	Right Left Left	Operation poorly performed because of intraventricular bleeding; immediate postoperative condition satisfactory	1/19/40	Fontanel soft and depressed but progressive downhill course marked by opisthotonos; pressure relieved	Died 1/19/40 in hospital, 20 days after operation; fontanel depressed; opisthotonos extreme

* In the 7 cases in group 2, which comprise 35 per cent of the entire series, 17 operations were performed.

have been converted into a success if I had followed up the first operations more aggressively and reoperated on the two sides in the hope of destroying additional portions of choroid plexus, as I learned to do in subsequent cases.

CASE 3.—L. P., a 3 month old boy, was referred to the Neurological Institute by Dr. Henry Kaessler, of Mount Vernon, N. Y. The child had had a generalized convulsion on July 2, 1940 and another on September 7, after which it was observed that the fontanel was tense and bulging and the neck rigid. A spinal tap yielded turbid fluid, containing 2,900 leukocytes per cubic millimeter. Organisms were not demonstrated in the spinal fluid by microscopic examination or by culture; chemotherapy was instituted, however, and the signs of inflammation

Fig. 3.—Seven children, or approximately 35 per cent, of my series survived operation, but were not permanently benefited. The children of this group are here pictured after operation and before discharge.

Upper row, left to right: J. B. (case 1, group 1); C. O. (case 2, group 1); L. P. (case 3, group 1). Lower row, left to right: R. M.. (case 4, group 1); J. C. (case 5, group 1); T. M. (case 6, group 1); H. F. (case 7, group 1).

The postoperative course in each case is given in the individual protocols in the text ("group 2").

disappeared. Nevertheless, the fontanel continued to be tense and bulging, and the head continued to grow. On admission the circumference of the head was 18½ inches (47 cm.). Indigo carmine injected into the right lateral ventricle was recovered from the lumbar sac after twenty-two minutes.

Operations.—On September 19, with the patient under anesthesia induced by avertin with amylene hydrate, the choroid plexus in each lateral ventricle was

cauterized. Destruction of the plexuses was thought to have been thorough, but there was a rapid return of intracranial tension.

On October 18 reexploration was performed bilaterally. This revealed that at the first operation both choroid plexuses actually had been thoroughly destroyed. Practically nothing remained except a thin white cord of scar tissue along the floor of the lateral ventricle on each side.

The child was discharged from the Neurological Institute on November 7, somewhat improved (fig. 3), but was subsequently admitted to the Jamaica Hospital with the anterior fontanel full and bulging. When seen there on May 1, 1941 the patient was in general good health. The fontanel at this time was soft but was definitely larger than when the child had been operated on. The head measured 21¼ inches (54 cm.) in diameter.

In this case interference with the normal movement and absorption of the cerebrospinal fluid due to postmeningitic adhesions was probably greater than in the typical case of congenital communicating hydrocephalus. Although the intracranial tension was not reduced to an entirely normal level, it was considerably lessened. If in all cases of postmeningitic hydrocephalus treatment along the lines herein laid down is instituted, a certain number of patients will certainly be saved, an observation proved by the outcome in another case (case 8, group 3).

CASE 4.—R. M., a 4 year old boy, had had a large and growing head since birth. Two weeks before admission to the Neurological Institute, in June 1937, severe headache, nausea and vomiting developed. On admission he appeared ill. His head measured 24¾ inches (63 cm.) in diameter. The results of the dye test indicated no obstruction.

Operations.—The right choroid plexus was cauterized on June 30, with temporary improvement. Because of recurrent symptoms the left plexus was cauterized on November 11.

Postoperative Course.—The patient was discharged, improved, on December 31, with apparently normal intracranial pressure (fig. 3). He was not brought back to the follow-up clinic at the end of the first month, as directed, but the mother appeared at the clinic and reported that the scalp was still sunken in over the two trephine openings. The child again failed to appear in the clinic two months after discharge. Investigation at this time disclosed that he had died a few days before of a short febrile illness. The mother stated that for six weeks before death, until the onset of the acute febrile illness, the child had seemed unusually well and bright, and the decompressive, operative areas had been soft and somewhat depressed.

Death in this instance appeared to be due not to any return of intracranial tension but to a late intercurrent infection.

CASE 5.—J. C., a 7 week old boy, had a tense fontanel and a markedly enlarged head when admitted to the Neurological Institute, on Aug. 7, 1937. The maximum circumference of the head was 17¾ inches (45.2 cm.). The results of the dye test indicated that he had communicating hydrocephalus.

Operations.—On August 8 satisfactory cauterization of the right choroid plexus was carried out, with the patient under anesthesia induced by avertin with amylene

hydrate. On November 13 this operation was carried out on the left side. Both operations were well tolerated.

Postoperative Course.—When the child was discharged from the hospital, on November 27, fourteen days after the second operation, he seemed to be in excellent condition. The anterior fontanel was depressed, the parietal and frontal bones were overriding and the head was considerably smaller than before the last operation. An excellent result was foreseen (fig. 3).

This child was admitted to the Morrisania City Hospital four days later with full blown bronchopneumonia, and he died of this disease on December 13.

The intracranial tension was actually reduced to normal or below normal by the operations. The disease, however, had so weakened the resistance of the child that he succumbed rapidly to an intercurrent infection.

Case 6.—T. M., a 12 week old boy, was admitted to the Neurological Institute on Dec. 8, 1937; he was ill, with an advanced degree of hydrocephalus.

Operations.—On December 30, with the patient under anesthesia induced by avertin with amylene hydrate, the right choroid plexus was cauterized and on Jan. 13, 1938 the left plexus. The patient had minimal reactions to the procedures.

Postoperative Course.—At the time of discharge, on January 22, nine days after the second operation, the child appeared to be in excellent condition. The vital signs were all normal. He was alert and active, was taking nourishment well and was sleeping well. The fontanel was markedly depressed, the cranial bones were slightly overriding and the circumference of the head was 3 cm. smaller than it was prior to the last operation. A most favorable course was anticipated (fig. 3).

On February 14 the fontanel was still depressed and the cranial bones were overriding. The circumference of the head was exactly the same as at the time of discharge, three weeks before. However, the baby was very weak and appeared to have lost weight. The mother stated that he would not take his feedings. The possibility of pyloric stenosis was considered and a prescription given for this condition.

The mother failed to keep the next three appointments in the follow-up clinic. Investigation then disclosed that the child had died at home during the month of April, four months after discharge from the hospital. There was no evidence of a recurrence of increased intracranial pressure; the child apparently died of general debility.

Once again, so far as can be determined, death was the result of low vitality and general debility produced by the illness and was not directly attributable to any return of intracranial tension.

Case 7.—H. F., a 7 month old Negro boy, was admitted to the Neurological Institute on Oct. 17, 1940 because of an enlarging head and convulsions. The results of the dye test did not indicate an obstruction.

Operation.—On November 14, with the patient under anesthesia induced by avertin with amylene hydrate, attempts were made to cauterize the choroid plexus in the lateral ventricles. But the trephine openings were badly placed so far as exposing the choroid plexuses was concerned, and in the effort to reach as much as possible of the structures trauma was inflicted, with resultant bleeding within the ventricle, so that visibility was still further reduced. As a result of all this, only about 35 to 50 per cent as much choroid plexus was cauterized as usual.

On December 29 a more thorough cauterization was attempted. This time a huge subdural (postoperative) hygroma was discovered; it had almost completely collapsed the lateral wall of the right ventricle and made operative procedures with the endoscope inside the right lateral ventricle impossible. On the left side, however, a moderately satisfactory cauterization of the plexus was carried out.

Postoperative Course.—The operation was well tolerated by the infant, and the fontanel thereafter always remained markedly depressed (fig. 3). The child did not do well, however. He refused to take his feedings and became increasingly weaker, drowsy and stuporous. As time passed there developed an increasing tendency toward muscular spasms and opisthotonos. On the twentieth postoperative day the child died. Permission for autopsy was refused.

In spite of a marked and sustained reduction in the intracranial pressure this child's course was slowly downhill after the operation, and he died of an unknown cause.

GROUP 3: TEN CASES IN WHICH THE PATIENT SURVIVED OPERATION AND THE OUTCOME WAS FAVORABLE

CASE 1.—A. O., a 1 month old boy, already had a greatly enlarged head when he was admitted to the New York Post-Graduate Medical School and Hospital on Jan. 6, 1934 with acute fulminating hydrocephalus. The maximum circumference at that time was 25 inches (63.5 cm.). The fontanel was widely open, tense and bulging. The results of the dye test indicated that he had nonobstructive hydrocephalus.

Operations.—On January 17, with the patient under ether anesthesia, the right choroid plexus was cauterized, and on July 10 the left plexus was destroyed. Between the two operations the child had bilateral purulent otitis media and varicella.

Postoperative Course.—The child was discharged from the hospital on July 17 in good condition, with the fontanel soft and depressed and the head slightly smaller than on admission. In February 1935, seven months after discharge, he was able to sit up in a high chair, to crawl and to repeat words. He lived for five years from the time of his first operation and finally died, of an intercurrent infection secondary to general debility, in January 1939 (fig. 4).

In this case, the first in which I performed the operation, the intracranial tension was markedly reduced by the operations, though not to an entirely normal level. If this patient had been encountered later, I should certainly have reoperated, with the hope and probability that I could find and cauterize additional portions of the two plexuses missed at the original operations and thereby reduce the intracranial tension to an entirely normal level.

Although a complete "cure" was not obtained, the fact that such a fulminating initial hydrocephalus was almost completely arrested for five years has caused me to regard the outcome in this early case as "satisfactory."

CASE 2.—A. V., a 5½ month old boy, was admitted to the New York Post-Graduate Medical School and Hospital on Feb. 5, 1935 with well advanced hydro-

cephalus. The fontanels were widely open, tense and bulging. The maximum circumference of the head was 20¾ inches (52.5 cm.). The results of the dye test indicated that he had a communicating type of hydrocephalus.

Operations.—On February 14, with the use of local infiltration with procaine hydrochloride, cauterization of the right choroid plexus was performed, and on March 7 a similar operation was carried out on the left side. The infant stood both operations extremely well.

Postoperative Course.—The postoperative complications were interesting. The child arrived back in the ward from the operating room in excellent condition and remained so during the next two hours. Then he became pale and listless,

TABLE 3.—*Data for the Ten Cases in Group 3, in Which the Patient Survived Operation and the End Result Was Favorable* *

Case No.	Patient	Date of Operation	Side Operated On	Present Status	Survival Period, Years	Mental Status
1	A. O'C.	1/17/34 7/10/34	Right Left	Died (1/19/39)	5	Mentally deficient
2	A. V.	2/19/35 3/ 7/35	Right Left	Living	6 4/12	Mentally deficient
3	K. G.	7/10/36 8/20/36 6/25/37 5/ 6/41	Right Left Right Left	Living	4 11/12	Moderately retarded
4	E. H.	10/11/36 2/ 2/37 10/20/37 1/29/38	Right Left Right Left	Living	4 8/12	Mentally deficient
5	R. C.	7/27/37 8/11/37	Right Left	Living	3 11/12	Moderately retarded
6	M. A. T.	11/18/38 12/ 6/38 7/19/39 7/19/39	Right Left Right Left	Living	3 7/12	Normal
7	A. J.	4/22/39 4/22/39 5/ 6/39 5/ 6/39	Right Left Right Left	Living	2 1/12	Normal
8	J. K.	5/26/39 5/26/39	Right Left	Living	2	Moderately retarded
9	F. R.	9/ 9/40 9/ 9/40	Right Left	Living	8/12	Normal
10	M. S.	11/12/40 11/12/40	Right Left	Living	6/12	Normal

* In the 10 cases in group 3, which comprise 50 per cent of the entire series, 28 operations were performed.

and the respirations became shallow and irregular, about every fifth or sixth one being sighing. The respiratory rate remained 16 per minute, but the patient was strikingly cyanotic. The pulse remained regular and the rate 100 per minute. The temperature was not particularly elevated.

At that time it was observed that the anterior fontanel was strikingly depressed. A lumbar puncture needle was thereon inserted through the widely open anterior fontanel into the lateral ventricle. When the stylet was removed from the needle, one could hear the air being sucked into the ventricle. Physiologic solution of sodium chloride was then infused into the ventricle by gravity until the fontanel was again flush with the rest of the cranial contour. The child's condition quickly improved. A similar state of acute intraventricular hypotension with alarming

symptoms occurred again on each of the two successive days and was relieved by introducing physiologic solution of sodium chloride into the ventricles.

The child was discharged from the hospital on April 16, nine days after the second operation, much improved (fig. 4). At this time the anterior fontanel was soft and depressed. Unfortunately, the parents moved out of the state almost immediately, without leaving any forwarding address, and I never had the opportunity of seeing the patient again.

Fig. 4.—These are the first two children on whom I operated. While the results in the early cases are not ideal, nevertheless they may be regarded as "satisfactory."

Upper row: A. O. (case 1, group 3). The photographs were taken at the time of discharge from the hospital in 1934 and again several years later. The child, originally afflicted with fulminating and rapidly advancing hydrocephalus, lived for five years after his operation.

Lower row: A. V. (case 2, group 3). The photographs were taken at the time of discharge and again several years later. The child was still living at the time this paper was prepared, six years after operation.

The case histories of these children are given in some detail in the text ("group 3").

About six months ago, however, the father appeared, seeking advice. He reported that the fontanel had stayed soft for nearly five years after the child left the hospital. During that time he had enjoyed general good health, had become ambulatory and, according to the father, was mentally bright (fig. 4). A few months before the father's visit, however, intracranial tension had again increased, and intermittent bouts of headache, vomiting and drowsiness were occurring. The father wanted to know how to treat these symptoms. He was urged to bring the child back to the hospital, and this he promised to do. The mother, however, would not allow this to be done.

When last heard from, at the time this compilation was started, the child was a complete invalid though still alive.

This infant had an advanced grade of hydrocephalus when treated and probably extensive damage to the brain. Under the circumstances, therefore, a six year survival may be considered a fairly satisfactory result. On the other hand, had I been able to see this child at occasional intervals after discharge I certainly should have reoperated on him, with the hope of achieving a far better functional result.

The case has additional interest because of the postoperative course, during which acute intraventricular hypotension developed which imperiled the child's life and had to be relieved by the infusion of Ringer's solution into the ventricles by needle in order to raise the pressure to a normal level. Had this not been quickly done, death probably would have resulted. This is the first case in my series in which the patient was so treated and recovered. There were similar reactions in case 1 of group 1 and case 9 of group 3.

CASE 3.—K. G., a 5 month old boy, was admitted to the Post-Graduate Medical School and Hospital on June 6, 1936. At that time the fontanel was widely open, bulging and tense (fig. 5). The maximum circumference of the head was 21½ inches (54.6 cm.). The results of the dye test indicated that he had a communicating type of hydrocephalus.

First and Second Operations.—On July 10, with the use of local anesthesia temporarily supplemented with ether anesthesia, the right choroid plexus was cauterized, and on August 20 a similar procedure was carried out on the left side. In spite of this the head continued to enlarge, although at a much slower rate than before the operations. Accordingly, he was again hospitalized (this time at the Neurological Institute) and on June 26, 1937, with the patient under anesthesia induced by avertin with amylene hydrate, endoscopic reexploration of the right choroid plexus was carried out. This showed marked destruction of the choroid plexus for about 1 inch (2.5 cm.) of its length, but the remaining portions showed no signs of having been touched at the previous operation. These undamaged parts were thoroughly cauterized.

Postoperative Course.—This child was seen in the follow-up clinic in March 1941, four years and nine months after his first operation. At that time he was alert, physically active, pleasant and apparently rather quick at understanding; he talked a great deal and with a rather subtle sense of humor. His head was half an inch (1.3 cm.) larger in maximum circumference than it had been three years before (fig. 5). The two small decompressed areas on each side of the

head were soft. His parents thought him mentally bright in his behavior at home but admitted on being questioned closely that he did not stand well in his classes at kindergarten. He rides a tricycle and takes part in all games.

Psychometric Report.—The following psychometric report was made by Miss Gladys Tallman in March 1941: "On this occasion Kenneth entered the examining room alone and willingly seating himself promptly at the little table. He was

Fig. 5.—The children in 2 early cases falling into the group with a favorable end result (group 3). Both children were living at the time this paper was written.

Upper row: K. G. (case 3, group 3). The photographs were taken before operation, in 1936, and again in March 1941, four years and nine months later.

Middle row: E. H. (case 4, group 3). This child had a large lumbar meningocele which had to be removed before the hydrocephalus could be treated. The huge defect in the skin of the back was closed by means of a pedicle graft, supplemented by pinch grafts taken from the amputated sac.

Lower row: E. H. (case 4, group 3). The patient is shown a few minutes after cauterization of the right choroid plexus and again today, four years and six months after operation. (See also figure 6.)

friendly, talkative and cooperative, although he tired quickly. He wasted some energy chewing gum. The mother reports that she sent the boy to kindergarten in February, but after one week the teacher asked that he be taken out of school because he was unable to cooperate. However, in that short time he learned to dress and undress himself. He is well behaved at home and congenial with the children of the neighborhood. Kenneth likes to listen to 'swing' music on the radio and knows the names of all the orchestra leaders and their theme songs. This child has been tested five times over a four year period. On the first test adequate scores could not be obtained because of his complete refusal to cooperate. At the times of the second and third tests cooperation was not too good, but intelligence quotients of 63 were obtained. In the last two tests cooperation was much better, no tests were refused and intelligence quotients of 67 on the Stanford-Binet scale were obtained. The child does his best work on verbal material. Kuhlmann-Binet, Stanford-Binet forms L and M, and Merrill-Palmer tests were used. According to all tests the boy is sufficiently retarded to be considered defective, but such interpretation of his development should be reserved until one other battery of these tests has been given. He tires quickly, and it may be that he is not working up to his capacitiy and that an adequate estimate of his intelligence has not yet been obtained."

Third Operation.—About May 1, after the material for this paper had been assembled, the patient received a severe blow to the head. Thereafter he became acutely ill, with severe headache, nausea, vomiting and stupor, and the decompression areas became bulging and very tense. Accordingly, reoperation was decided on, and on May 6, with the patient under anesthesia induced by avertin with amylene hydrate, endoscopic reexploration of the two lateral ventricles was performed. This showed complete destruction of the plexus in the right ventricle, there being only a linear scar to mark the original site of the plexus. The plexus in the left ventricle, however, was essentially normal in appearance. It was obvious that the original cauterization on this side had been far from complete. At this session thorough destruction was accomplished.

Course After Third Operation.—The postoperative course was unusually stormy and of special interest. The child tolerated the operation itself well and was returned to the ward in good condition. Some hours later, however, he became fretful and showed increasing signs of irritability, associated with "showers" of fine and coarse tremors and a fluctuating spastic state. These symptoms were accompanied by high fever and sterile meningitis. It should be noted that the tremors were bilateral and generalized, although only the left choroid plexus had been cauterized. This complication persisted for many days before the patient got better, but at this writing intracranial tension is once more at a normal level.

This was the first case in my series in which the patient was reoperated on. The importance of doing this was amply revealed. At the second operation it was found that while a part of the right choroid plexus had been completely destroyed at the first operation there still remained sizable portions of the plexus which, though easily accessible, had for one reason or another escaped the cautery. At the third, and last, operation (the second carried out on the left side) a similar situation was found on the left side. Had I been quicker and more aggressive in reoperating this patient, in addition to normal intracranial tension, undoubtedly would have a far better psychometric rating today.

This case is most instructive, therefore, in showing the necessity of following the patient closely and reoperating early if signs of pressure do not abate or, having temporarily abated, recur. The lesson here learned was applied profitably in case 6 and, to even more striking effect, in case 7 of this group.

The case is also of interest for the reason that after the last operation there occurred the same belated, bilateral and generalized twitchings and spastic states that occurred in 2 of the fatal cases (cases 1 and 2 of group 1). The appearance of the twitches in this case takes on special significance because this was the first time this phenomenon has been observed since the introduction, in June 1937, of the buffered Ringer's solution ("artificial spinal fluid") for irrigation of the ventricle during the operation and, singularly, was also the first time since that date that ordinary Ringer's solution had been used instead of the buffered solution. This case, therefore, adds some support to the theory advanced earlier in this paper that unbuffered Ringer's solution when substituted in any large quantity for cerebrospinal fluid is irritating and that the buffered solution is decidedly less irritating and correspondingly reduces the incidence and severity of postoperative reactions.

CASE 4.—E. H., a 2 month old girl, was admitted to the New York Post-Graduate Medical School and Hospital on Oct. 11, 1936 with hydrocephalus and a huge lumbar meningocele. The maximum circumference of the head was 17¾ inches (44.4 cm.). The results of the dye test indicated that she had a communicating type of hydrocephalus. The meningocele was first excised and the defect in the skin repaired by a plastic procedure (fig. 5), after which the hydrocephalus was treated.

Operations.—The right choroid plexus was cauterized on November 1, with the use of local anesthesia supplemented with very light primary inhalation of ether. The child withstood the procedure extremely well (fig. 5) and was discharged twelve days later with the fontanel depressed. After a while, however, the head again started to enlarge disproportionately, and on Oct. 19, 1937 she was admitted to the Neurological Institute, at which time the maximum circumference of the head was 22 inches (55 cm.).

The left choroid plexus was cauterized on October 20, with the patient under anesthesia induced by avertin with amylene hydrate. The procedure was rather unsatisfactorily carried out because of some traumatic bleeding, and I estimated that about one half of the accessible part of the plexus was left untouched.

The right choroid plexus was reexposed on Jan. 29, 1938, with the patient under anesthesia induced by avertin with amylene hydrate. At this time it was found that the anterior one third of the exposed plexus had been completely destroyed at the earlier operation on this side, so that only a thin white band of scar tissue was left, but that the posterior two thirds had apparently not been touched. Thorough cauterization of this portion was effectively carried out at this session. The patient tolerated the procedure well and on February 14 was once more discharged, with the fontanel soft and depressed.

Postoperative Course.—After discharge an unusual sequence of events took place. The fontanel remained flat for about one week and then suddenly became

extremely tense. The child was hurriedly brought back to the Neurological Institute. The results of the dye test performed at this time indicated that the infant had marked obstructive hydrocephalus, whereas prior to operation she had had nonobstructive, or communicating, hydrocephalus. It was assumed, therefore, that a fragment of devitalized choroid plexus had broken off and drifted into the narrow aqueduct of Sylvius, where it had caused acute obstruction. Palliative ventricular taps were performed daily, in the hope that the offending fragment would soon be absorbed or, at least, dislodged from the aqueduct. After many days of tapping the intracranial tension suddenly failed to return, and the fontanel remained soft. Ventriculograms made at this time revealed a considerably thicker cerebral cortex than was shown at the time of her first admission to the Institute, in October 1937 (fig. 6). Since then there has been no evidence of a return of increased intracranial pressure.

The child was last seen in March 1941, at which time she was readmitted to the Neurological Institute for a brief period of observation (fig. 5). At that time there were no symptoms or signs of increased intracranial tension. A lumbar

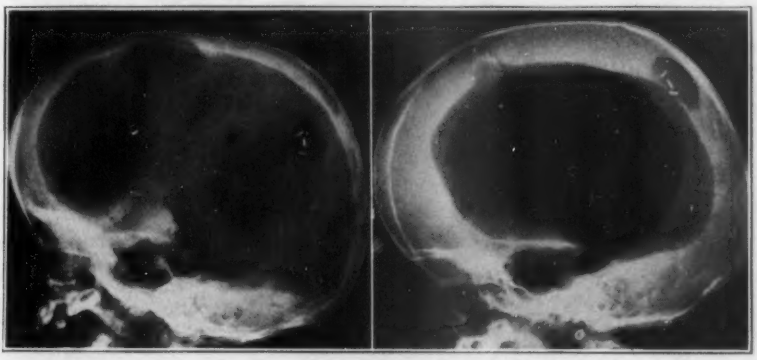

Fig. 6.—Ventriculograms in case 4, group 3, before and after cauterization of the choroid plexus. Observe that the cortex is much thicker in the later picture than in the earlier one. This suggests that some degree of cortical regeneration may be possible after intraventricular pressure has been relieved.

puncture needle was introduced into the right lateral ventricle and the intraventricular pressure tested. This proved to be entirely within normal limits. Unfortunately, however, complete arrest of the intraventricular pressure was not achieved in this child until permanent, irreparable damage had been done to the brain.

Psychometric Report.—The following brief psychometric report was made by Miss Gladys Tallman, chief psychologist, in March 1941: "This child has been seen twice in the last thirteen month period. The Kuhlmann-Binet and Gesell scales have been used in testing her. In her first test her age measured 16.8 months and in her second 14.4 months on the first-named material. On the Gesell material she scored about 15 months in language development and between 8 and 12 months in other accomplishments. There was a visual difficulty, and she was not in particularly good physical condition. She seems to be seriously retarded and is probably defective in mental development."

This case demonstrates clearly, once again, that in almost every one of the earlier operations only a fraction of the surgically accessible choroid plexus was actually destroyed. The moral to which this points is that patients need to be followed closely after operation so that any return of intraventricular tension may be noted and the patient be reoperated on immediately, if it develops, before permanent damage is done to the cortex by the pressure. Had reoperation been performed without delay in this case, a far better intelligence rating would certainly have been attained.

In this case there was also observed for the first time the temporary conversion after operation of nonobstructive (communicating) hydrocephalus into the obstructive type, and a subsequent final return to the original nonobstructive type. This was later observed in another case (case 6, group 3). The probable explanation is that a piece of coagulated choroid plexus broke off and found its way into the narrow aqueduct of Sylvius, which it partially plugged until it was dislodged or dissolved. Until the aqueduct had again become free reduction of the intraventricular pressure by means of daily ventricular taps was necessary.

Finally, the ventriculograms indicate that the cortex became thicker after the destruction of the choroid plexus and the consequent reduction of intraventricular tension. So far as is known, this observation has never before been reported. The increased thickness of the cortex implies, though of course does not prove, that there was a regeneration of damaged cortical tissue after the pressure was relieved.

CASE 5.—R. C., a 3 month old boy, was admitted to the Neurological Institute on July 24, 1937; his head measured 20½ inches (52 cm.) in diameter. The anterior fontanel was huge, measuring 8 by 4 inches (20 by 10 cm.), and was bulging and tense. The results of the dye test indicated that he had communicating hydrocephalus (fig. 7).

Operations.—On July 27, with the patient under ether anesthesia, the choroid plexus in the right lateral ventricle was cauterized, and on August 8 a similar operation, this time with the use of anesthesia induced by avertin with amylene hydrate, was carried out on the left side. Both procedures were well tolerated.

Postoperative Course.—The patient left the hospital on August 17, with the fontanel slightly depressed. He has had, so far, permanent reduction of intracranial tension to a normal level. From the physical standpoint, he appears to have made an excellent recovery. He was last seen during March 1941 (three years and nine months after his first operation) and at that time he was physically active. His head measured 22 inches (56.0 cm.), an increase of only 1½ inches (7.5 cm.) in over three and a half years. There did not appear to be any disproportion at this time between the head and body; in fact, the child had a very attractive appearance (fig. 7).

Mentally, also, he seemed alert in most respects. He said his A, B, C's and counted to 100 correctly. He talked a great deal and put together fairly sizable sentences. He even sang a number of songs rather well. Although the mother

complained that he was wilful and destructive, he was pleasant, interested and cooperative during the entire time that I was examining and photographing him (fig. 7).

Psychometric Report.—The psychometric report, made by Miss Gladys Tallman, however, is not so encouraging: "This child has been seen three times over a

Fig. 7.—Ten (50 per cent) of the 20 children on whom I operated have had results which may be regarded as satisfactory. Individual protocols of the cases of these patients are given in the text ("group 3").

Two of these children for whom the result was favorable are pictured here, before and after operation.

Upper row: R. C. (case 5, group 3) before operation and today, three years and nine months later.

Lower row: M. A. T. (case 6, group 3) at time of operation and as she appears today, three years and five months later.

In the case of M. A. T., pressure was not arrested after the first operation and failure seemed certain, but after the second operation, in which additional plexus was destroyed, the pressure became normal. Today she is very bright and presents one of the best results. She illustrates well the importance of reoperation if pressure is not relieved by the original operation.

fifteen month period and at no time has satisfactory work been obtained from him. He has been badly spoiled by his family and is wilful and most difficult to control. He is destructive with all test toys and swears like a trooper at the examiner. Left to his own devices he sings many popular songs, carrying the tunes well, showing a good sense of rhythm and remembering most of the words. When displeased he runs to the wall, bangs his head against it and then cries. The Kuhlmann-Binet, Stanford-Binet, Merrill-Palmer and Vineland social maturity scale tests have been used. His successes have been occasional and varied, on tests of the second and third year levels. He gives a superficial impression of being mentally bright, although prolonged observation suggests serious retardation. Emotional factors, however, confuse the picture at this time."

From purely physical and physiologic standpoints an excellent result has been obtained in this case.

Unfortunately for the child's intellectual development, his home situation is extremely bad. The mother is incapable, by endowment or education, of handling him, and he rules her and the household tyranically by means of temper tantrums. Such tantrums completely disrupted the psychometric examinations on several occasions. However, when I saw the youngster in my office an hour before such an examination, he was pleasant, alert and cooperative. He was almost "impish" and certainly well satisfied with himself. One gets the impression at such times that his intelligence quotient is not far from normal. It is planned to hospitalize this child in the future, to study his emotional behavior and to see if discipline will not improve his performance in the psychometric tests.

CASE 6.—M. A. T., a 4 month old girl, was admitted to the Neurological Institute on Oct. 27, 1938 with a diagnosis of hydrocephalus. The maximum circumference of the head was 19 inches (47½ cm.). The fontanel was widely open, tense and bulging. The frontal bosses were conspicuously prominent. The results of the dye test indicated that she had a communicating type of hydrocephalus.

Operations.—On November 18, with the patient under anesthesia induced by avertin with amylene hydrate, the right choroid plexus was satisfactorily cauterized. On December 6 a similar procedure was performed on the left side. The child withstood both procedures well and was discharged on December 24, greatly improved and with the anterior fontanel soft and depressed (fig. 7). After discharge the fontanel remained soft and depressed for over six months and then gradually began to bulge again and occasionally to become tense. Because of this, on July 13, 1939 the child was readmitted to the Institute.

On July 19, with the patient under anesthesia induced by avertin with amylene hydrate, the choroid plexuses in both lateral ventricles were reexplored at one operative session. On each side it was found that the anterior half of the visible and accessible portion of the plexus had been completely destroyed and reduced to a thin white band of scar tissue but that a great amount of choroid remained, apparently untouched, in the region of the atrium of the ventricle at the "knee" of the plexus. This was thoroughly cauterized on both sides at this time.

Postoperative Course.—The immediate postoperative course was interesting and instructive. Although a large amount of plexus had been destroyed in each lateral ventricle, the intracranial tension the day after the operation was much greater than it had been before. Because of the experience with the patient in case 4 of this group, dye was immediately introduced into one of the lateral ventricles. This did not appear in the lumbar sac for forty minutes, although prior to operation it had appeared in fifteen minutes. The inference, as in the case previously cited, was that a fragment of devitalized plexus had floated into the narrow aqueduct of Sylvius and obstructed it. Ventricular taps sufficient to reduce the tension were performed daily for nearly five weeks. At first the fluid obtained was turbid and xanthochromic and had high total protein content, but as time went on it gradually became normal in appearance. Finally the intracranial tension became normal, and in a repetition of the dye test the dye was recovered from the lumbar sac after fifteen minutes. The child was finally discharged from the hospital on September 12, much improved and with the anterior fontanel soft and depressed.

The subsequent progress of the child has been most gratifying. All symptoms and signs of intracranial pressure have completely disappeared. The head looks essentially normal. She has developed physically and is very active. Mentally she is unusually bright and attractive. She talks glibly and knows a large number of isolated facts. She has memorized most of the Mother Goose rhymes, and has a repertoire of songs, many of which are current popular favorites (fig. 7).

Psychometric Report.—A psychometric report by Miss Gladys Tallman was as follows: "This child has been tested three times over a fourteen month period. At all times she has been friendly and most cooperative. All test scores have shown a slight acceleration over her chronologic age. Her intelligence quotients have varied from 105 to 103. Her speech is well developed. The Kuhlmann-Binet, Stanford-Binet forms L and M, Gesell rating scale, Merrill-Palmer and Vineland social maturity scale tests have been used."

This case teaches several lessons. First, it again demonstrates the importance of a persistent follow-up study, with early reoperation if intracranial tension redevelops. These tactics in this case converted an initial failure into the most successful outcome of the series.

Second, it offers a second good example of one important postoperative complication (encountered originally in case 4 of this group), namely, the temporary "plugging" of the aqueduct of Sylvius by fragments of devitalized choroid plexus floating free in the ventricular fluid, and it reveals how this complication may be successfully handled by daily ventricular taps.

Finally, this case demonstrated the advantage of the occipital approach to the plexus, which enables the operator to reach and destroy the heavy "knee" of the plexus. It also proves the feasibility of cauterizing the plexus in each lateral ventricle at the same operative session.

CASE 7.—A. J., a 3 month old girl, was admitted to the Neurological Institute on April 20, 1939 with fulminating hydrocephalus. The fontanel was widely open, bulging and tense. The head measured 17 inches (43 cm.) in diameter (fig. 8). The results of the dye test indicated that the patient had a communicating type of hydrocephalus.

Operations.—On April 22, with the patient under anesthesia induced by avertin with amylene hydrate, the choroid plexus in each lateral ventricle was cauterized. The child withstood the procedure well, but there was not a very great reduction in the tenseness of the fontanel. Accordingly, on May 6, just two weeks after

Fig. 8.—Two more children in the group with a favorable end result (group 3).

Upper row: A. J. (case 7, group 3) before operation and today, two years after operation.

This child, like that in case 6, failed to respond well after her first operation but did extremely well after recauterization of the plexus. She has attained an essentially normal mental level for her age.

Lower row: J. K. (case 8, group 3). Before operation this boy was critically ill. Today, two years later, he is the picture of health. In this youngster communicating hydrocephalus developed after he had recovered from meningitis, treated successfully with sulfanilamide (fig. 9). This is the first case of its kind to be reported in which treatment by cauterization of the choroid plexus was successful.

the first operation, with the patient under anesthesia induced by avertin with amylene hydrate, endoscopic inspection of the two lateral ventricles was performed. This revealed that while great portions of both plexuses had been destroyed the destruction was "spotty" and a large amount of healthy-looking choroid remained. Thorough recauterization of the remaining parts of the plexuses was thereon carried out. The child tolerated this procedure extremely well.

Postoperative Course.—Since the last operation there has been no suggestion of increased intracranial tension. The child did not start to walk until she was 18 months old, but she now walks and runs better than most children of her age. She is a particularly attractive child, alert, pleasant, well mannered and socially well adjusted. Her mother feels that she is normal in all respects (fig. 8).

Psychometric Report.—The psychometric report by Miss Gladys Tallman was as follows: "This child is a nice-looking little girl of apparently average mental development. She was, on the whole, friendly and cooperative, though occasionally a bit wilful during the test. She showed retardation of three months on Stanford-Binet material and four months on Kuhlmann-Binet and Merrill-Palmer material. On the Vineland social maturity scale she measured at least up to age. Considering that she was born two months prematurely, had been desperately ill for the first three months of her life and then underwent two serious operations with prolonged convalescence after each, the mental development is really extremely good. An even higher rating may be confidently expected in future tests."

The outcome in this case is one of the most successful in my series. I had learned in the earlier cases the importance of reoperation when the patient did not improve as had been expected after the first operation and in this case I waited only two weeks before reoperating. The extremely favorable result which followed the supplementary cauterization well justified the procedure and established the importance of early reoperation in all cases in which the reduction of intracranial tension after the initial operation is not immediately satisfactory.

This case also demonstrated again the feasibility of performing bilateral cauterization in a single session.

CASE 8.—J. K., a 2 year old boy, was referred to the Neurologic Institute on May 8, 1939 by Dr. Henry A. Riley. He had developed normally and had been entirely well until Jan. 23, 1939, when he had fallen from a second story window onto a cement pavement. He lost consciousness immediately and remained in this state for the next forty-eight hours. He was transported to a hospital, where a right temporoparietal decompression was performed. After this procedure there was gradual improvement in both the state of consciousness and the general vital signs.

About three weeks after his operation, on February 14, the child became acutely ill, with high fever and nuchal rigidity. A spinal tap yielded clear fluid containing 80 cells per cubic millimeter. The next day the spinal fluid contained 400 cells per cubic millimeter, but no organisms were seen in it and culture yielded no growth. At this time the right ear began to drain profusely, and cultures yielded Staphylococcus aureus haemolyticus and hemolytic streptococcus. Examination revealed tenderness over the right mastoid. He was treated intensively with sulfanilamide. Gradually the temperature subsided, the ear stopped draining and the signs of

meningitis cleared up. The cells disappeared from the spinal fluid, and all signs of sepsis disappeared. Organisms were never demonstrated in the spinal fluid.

After the child's recovery from this septic state the temporoparietal decompression area became increasingly tense and began to bulge. As time went on the bulging increased to an alarming degree, and the child showed signs typical of acute and excessive intracranial tension. He was transferred to the Neurological Institute, critically ill (fig. 8). He could hardly be aroused. The decompression was bulging greatly and was very tense. It was thought, on the basis of the history, that he was suffering from postmeningitic hydrocephalus. Neutral indigo carmine introduced into the lateral ventricle was recovered in large amount from the lumbar sac after fifteen minutes, which indicated that he had a free communicating type of hydrocephalus.

A ventriculographic examination was performed, in which 200 cc. of cerebrospinal fluid was fractionally withdrawn and an equal amount of oxygen introduced into the lateral ventricles. The roentgenograms showed markedly dilated ventricles

Fig. 9.—Ventriculogram in case 8 group 3. This roentgenogram shows the degree of hydrocephalus which had already developed in the short time after the meningitis had been cleared and the hydrocephalus had begun. The hydrocephalus was arrested by cauterization of the choroid plexus in the two lateral ventricles, and the patient is today in excellent health (see fig. 8).

(fig. 9). After the roentgenograms had been taken the gas was slowly removed and replaced by the cerebrospinal fluid which had originally been removed and kept at body temperature. The child showed no serious change as a result of this procedure.

Operations.—On May 26, with the patient under anesthesia induced by avertin with amylene hydrate, the choroid plexus in each of the lateral ventricles was cauterized. The child withstood this procedure very well.

Postoperative Course.—Almost immediately after this operation there was noticeable improvement in the child's condition. The decompression area became soft, and all symptoms of increased intracranial tension subsided. He was discharged from the Neurological Institute on June 18, much improved.

Since his discharge from the hospital his physical condition has continued to be most satisfactory. There has been no evidence of increased intracranial tension.

He is active and very strong. When interviewed in March 1941 he appeared to be unusually bright and alert for his age (fig. 8).

Psychometric Report.—A psychometric report by Miss Gladys Tallman was as follows: "This boy has been tested three times over a two year period. When he was 2 years of age no satisfactory estimate of his mental development could be made because of his physical condition and his retardation in speech. His understanding of words seemed adequate. At 3 years of age he showed a retardation of twelve months on Kuhlmann-Binet material and thirteen months on Stanford-Binet material. Speech was still limited. At the time of his last test he became tired before the work could be completed, so that the score on the Stanford-Binet test was not adequate. However, there is evidence of acceleration in spite of this. A complete performance test was given, and on the basis of this test his developmental age ranged from 24 to 41 months. If his intelligence quotients are strictly interpreted, the boy would be characterized as a high grade moron. However, because of the recent change in his rate of growth and his tendency to quick fatigue, he should be classified as retarded and very likely to rate higher on later tests."

This appears to have been a case of frank postmeningitic hydrocephalus, although organisms were never actually demonstrated in the cerebrospinal fluid. The fact that there were 400 cells per cubic millimeter of spinal fluid indicates that meningitis existed, and whether or not organisms were present, pia-arachnoiditis and ependymitis must have occurred, with the usual postinflammatory meningeal adhesions. Hemolytic organisms were close at hand.

The patient has now been entirely free of symptoms for two years.

So far as I know, this is the first reported case of noncongenital, postmeningitic hydrocephalus successfully treated by cauterization of the choroid plexuses.

CASE 9.—F. R., a 2 month old Puerto Rican boy, was referred to the Babies Hospital at the Columbia Medical Center on Aug. 10, 1940 by Dr. Louis Rousselot. At the time of admission the child had a large lumbar meningocele and early hydrocephalus; the maximum circumference of the head was 16⅛ inches (41 cm.). At the end of three weeks, after the child had been studied and then operated on by Dr. Rousselot for meningocele, the circumference of the head was 17¼ inches (43.7 cm.), an increase of 1⅛ inches 2.8 cm.).

Operation.—On September 9, with the patient under anesthesia induced by avertin with amylene hydrate, the choroid plexus in each lateral ventricle was cauterized. The child withstood the procedure well.

Postoperative Course.—An interesting complication marked the immediate postoperative course. A few hours after the operation I was called to the ward because the child did not seem as well as previously. At this time the anterior fontanel was markedly depressed, being drawn sharply and forcibly inward. This had occurred in spite of the fact that throughout the operation care had been exercised to maintain a positive pressure within the ventricle by means of the irrigating system used in connection with my instrument and technic, so that when final closure was made the anterior fontanel was even slightly bulging. The child was restless, but the vital signs were not otherwise alarming. I remembered the events which occurred in case 2 (A. V.) of group 3; so preparations were made for

ventricular tap, with infusion of Ringer's solution. But the child's immediate condition did not seem severe enough to warrant this treatment at the moment, and as time passed the situation improved generally, so that this procedure was not necessary.

The patient was discharged on September 21. At this time the anterior fontanel was depressed and soft and the child's general condition was most satisfactory (fig. 10). A letter received from the mother in March 1941 (six months after operation) stated that the fontanel had remained depressed and soft and that

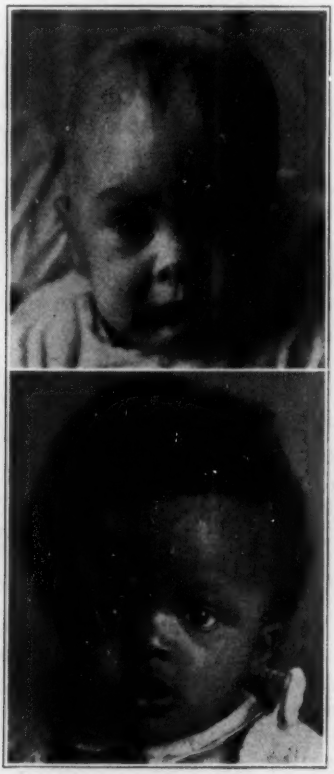

Fig. 10.—Children in 2 of the more recent cases in which results were favorable.

Upper row: F. R. (case 9, group 3) as he appeared when discharged from the hospital. His parents write from Central America, eight months after operation, that the fontanel is still depressed and the child is developing normally, both physically and mentally.

Lower row: M. S. (case 10, group 3). Six months after operation, when the photograph was taken, this little Negro girl had a soft, depressed fontanel and a normal intelligence for her age.

Complete protocols of these cases will be found in the text under the heading "group 3."

the head had not enlarged. She was delighted with the child's general physical condition and mental development. Since no word to the contrary has since been received, it is assumed that a favorable course continues.

Although only eight months has elapsed since this child was operated on, it appears that the rapidly advancing hydrocephalus has thus far been completely arrested and that normal physical and mental development is taking place.

CASE 10.—M. S., a 4 month old Negro girl, was admitted to the Neurological Institute on Oct. 10, 1940, because of her enlarged head. Its maximum circumference was 19⅞ inches (50.5 cm.). The anterior fontanel was widely open, tense and bulging. The results of the dye test indicated that she had a communicating type of hydrocephalus.

Operation.—On November 12, with the patient under anesthesia induced by avertin with amylene hydrate, the choroid plexus in each lateral ventricle was cauterized.

Postoperative Course.—The child tolerated the operation well and was discharged on November 24, much improved and with a soft, depressed fontanel. She was last seen during March 1941, at which time she seemed in all respects to be normal. The circumference of the head was the same as at the time of her discharge from the hospital, four months before. The fontanel was smaller and soft. There have been no signs of pressure. She sat up alone and was interested in all that went on about her. The psychometric examination at that time indicated normal mental development for a child of her age (fig. 10).

In this case operation was performed only six months ago, but the result to date is such as to warrant placing it in the group of cases in which the outcome was "satisfactory."

COMMENT

Group 1: Three Cases in Which Death Resulted from Operation.—The 3 operative deaths represent a case mortality of approximately 15 per cent, but it should be noted that they represent an operative mortality of only 6 per cent. It seems highly probable, also, that the death in case 3 should not properly be attributed to the operation itself. The evidence is overwhelming that the child actually died of acute cardiac decompensation resulting from an ill advised and badly given blood transfusion. If this is granted, the case mortality would be lowered to 10 per cent for the entire series and the operative mortality to approximately 4 per cent.

All 3 operative deaths occurred prior to June 1937. Since that date more discrimination has been used in the selection of patients, and since more skill has been acquired in the technical procedures, there has been no operative mortality.

In cases 1 and 2 of this group death undoubtedly was brought about by the operative procedure, and the result properly should be designated as an "operative death." A study of these cases reveals that they have in common three distinct and rather amazing features: 1. The signs of physiologic disturbance consisted chiefly of intermittent, tonic spasms. 2. These signs were bilateral and general and were not

referable to the one side of the brain which had been operated on. 3. They did not appear until hours after cauterization had actually been performed.

Had the fatal disturbance of the brain been caused by the electric current passing through it or by the heat engendered by the cautery, one would have expected some immediate reaction at the time cauterization was performed. Moreover, since cauterization in each of these 2 cases was performed only on the right side of the brain, one would have expected any convulsions, tremors or paresis to point sharply to the side of the operation. On the contrary, in these 2 cases there was a decided interval after the cauterization before the onset of the unfavorable signs, the interval being three hours in 1 case and six hours in the other, and lateralizing features were notably absent throughout the entire postoperative course in both cases. These facts led me to conclude that death in cases 1 and 2 was not the result of passage of the electric current through the brain or of the radiation of heat from the cautery.

The question then arose whether these disturbances and deaths could be due to chemical changes in the composition of the cerebrospinal fluid as a result of the operation. It will be noted that a rather constant irrigation of the operative field with physiologic solution of sodium chloride was maintained throughout the operation in these cases, in order to dissipate the local heat engendered by the cautery, to keep the visual and operative fields clear of blood and debris and to insure a continuous intraventricular pressure which would keep the thinned-out walls of the ventricles (the cerebral cortex) from collapsing. Because of the ease with which the cerebrospinal fluid escaped from the ventricle around the shaft of the ventriculoscope, several liters of irrigating fluid were used for this purpose in each operation. It seems reasonable to assume that this might have altered not only the mineral but the organic content of the cerebrospinal fluid to such an extent that it would become irritating, and even destructive, to the brain tissue with which it came into contact. This would have affected all parts of the brain in contact with the fluid.

Acting on the theory that these deaths were attributable, at least in part, to an alteration in the composition of the cerebrospinal fluid, in June 1937 I modified my technic in two respects: (1) For irrigation I employed instead of ordinary physiologic solution of sodium chloride a buffered Ringer's solution recommended by Dr. Ernest Sachs, sometimes referred to as "artificial spinal fluid," and (2) I used only the smallest amount of this fluid necessary to keep the operative field clear and prevent collapse of the ventricular walls. I felt that the new irrigating fluid might be expected to maintain the inorganic balance better than the physiologic solution of sodium chloride previously used

and that if trouble still occurred the help of the organic chemist should be sought for possible ways to offset the loss of organic elements in the intraventricular fluid.

Since the introduction of the buffered Ringer's solution, in June 1937, the average postoperatve course has been gratifyingly smooth, and I have had no operative deaths. This supports the idea that death in cases 1 and 2 was somehow due to changes induced in the composition of the cerebrospinal fluid during the operation rather than to the direct effect of the electric current or of the heat engendered by the cautery on the brain.

Acute intraventricular hypotension was encountered for the first time in case 1 of this group and undoubtedly contributed to the patient's death. This phenomenon was subsequently observed in 2 other cases, in which, fortunately, the patient survived (cases 4 and 9, group 3).

Group 2: Seven Cases in Which the Patient Survived Operation but the End Result Was Unfavorable.—In cases 1, 2 and 3 of this group the intracranial tension was never permanently reduced to a normal level. Failure in case 1 was due primarily to a short circuit in the instrument, which prevented satisfactory cauterization of the plexus. Failure in this instance, therefore, probably should not be blamed either on the rationale or on the technic of the operation. It seems probable that if a more aggressive attitude had been taken in case 2 and early recauterization performed with more thoroughness reduction of the intracranial tension to a normal level might have been obtained. This was done in some of the later cases (group 3) with gratifying results.

In case 3, on the other hand, all of the choroid plexus in the lateral ventricles which was surgically accessible was destroyed at the original operation, as was proved by reexploration. The imbalance between the rate of formation and the rate of absorption of the cerebrospinal fluid was simply too great to be equalized by destruction of the accessible portions of choroid plexus in the lateral ventricles. The fact that the hydrocephalus in this case followed meningitis may be significant, since it seems probable that the interference with the normal circulation and absorption of the cerebrospinal fluid in the ventricular and subarachnoid spaces due to postinflammatory organized exudates and adhesions might well be greater than the interference usually found with the simple congenital defects. However, in another case of postmeningitic hydrocephalus (case 8, group 3) a satisfactory balance was struck and the hydrocephalus was arrested.

In the last 4 cases of this group the patient died in spite of the fact that the intracranial pressure was definitely lowered by the operation to a normal, or possibly even to a subnormal, level.

The persistent and pronounced depression of the fontanel after operation in cases 5, 6 and 7 gives rise to speculation about whether the general debility might have been due, in part, to subnormal intracranial pressure resulting from too radical destruction of the choroid plexuses. In any event, it is true that in the last 4 cases of this group the operative measures were successful in reducing the intracranial tension.

In summary, therefore, it appears that a certain number of infants with hydrocephalus are encountered who despite survival of technically satisfactory operations succumb to the disease. These comprise about 35 per cent of the patients in my series. Death was due in some cases to persistence of intracranial tension caused apparently by an imbalance between the rate of production of the cerebrospinal fluid and the rate of its reabsorption so great that it could not be overcome by destruction of those portions of the choroid plexuses which were surgically accessible. In other cases of this group, in which the intracranial tension had been satisfactorily reduced to a normal level by operation, death appeared to be the result only of general weakness and debility.

Group 3: Ten Cases in Which the Patient Survived Operation and the End Result Was Favorable.—The 10 children of this group, comprising 50 per cent of all the patients treated, responded in a manner which may be considered satisfactory, in the sense that intraventricular pressure was reduced to essentially normal levels.

Nine of the 10 children are still alive, the longest survival period being over six years and the shortest six months. The 1 child of this group who has died was the first patient whom I operated on for this condition. Although this infant already had an advanced stage of hydrocephalus at the time of operation, in January 1934, the condition was strikingly arrested and he survived for a full five years before succumbing to intercurrent disease.

The most important lesson learned from this group of cases is the necessity of maintaining close postoperative contact with the patient and of reoperating at once if intracranial tension does not subside after operation or, once having subsided, recurs. Cauterization of a plexus may have appeared to be very thorough at the time it was done, but inspection of this same plexus a few weeks or months later may reveal that the destruction was in fact much less complete than had originally been thought. This may be due to several factors. In the beginning it was feared that the patients would not tolerate extensive cauterization; so the operation was carried out very cautiously. Today it is known that they tolerate the procedure very well, and consequently much more radical operations are now performed. Again, in my earlier cases the incision was placed too far forward to permit maximum visualization and cauterization of the "knee" of the plexus, where the bulk of the

choroid tissue is located. In my later cases I have placed the incisions more posteriorly, slightly superior and slightly lateral to the site usually employed for the trephine openings for ventriculographic examination. This approach makes it possible for a far greater part of the plexus to be reached and destroyed than did the earlier incision. Finally, if the plexus is very heavy and "fluffy" the more superficial and visible parts may be thoroughly cauterized, while the deeper parts may escape destruction. These points are all well illustrated by cases 3, 4, 6 and 7 of this group, especially cases 6 and 7, in which potential failure was transformed into success by following this principle of reoperation.

Radical operation is important if good results are to be obtained.

Acute intraventricular hypotension was an interesting postoperative complication in cases 2 and 9 of this group. In the former it constituted a major threat to the patient's life on several occasions and was relieved only by the infusion of Ringer's solution into the ventricle in amounts sufficient to elevate the intraventricular pressure to a normal level. In case 2 of group 1 acute intraventricular hypotension was a conspicuous factor contributing to the child's death.

Transformation of nonobstructive hydrocephalus into the obstructive type occurred in cases 4 and 6 after cauterization of the choroid plexus. This was brought about, presumably, by the breaking away of a small piece of dehydrated and cauterized choroid tissue from the plexus and its being carried by the cerebrospinal fluid circulation into the narrow aqueduct of Sylvius, where it produced a block. The degree of intracranial tension in case 4 was extreme and unquestionably would have resulted in the death of the child had not frequent ventricular taps been performed several times daily for a number of days. Eventually the offending tissue was dislodged from the entrance to the aqueduct by the mechanical effect of the taps or it was dissolved by natural processes, after which dye introduced into the ventricle again appeared promptly in the lumbar sac. Failure to recognize the mechanism producing the increased intracranial tension present after the operation and to take prompt and effective measures to relieve it temporarily would certainly have resulted in death in at least 1 of these cases. There seemed to be no delayed or late manifestation of hypotension in these cases or in any others.

Roentgen evidence of cortical regeneration was found in case 4. In this case ventriculograms showed the cerebral cortex to be considerably thicker a year after operation than it had been before, and this invites the belief, though it does not offer proof, that regeneration of cortical tissue may occur after an abnormally high intraventricular tension has been reduced to a normal level.

Postmeningitic hydrocephalus was successfully treated in case 8. So far as I know, this is the first case of this sort to be reported. With the

increasing use of the new forms of chemotherapy, more cases in which meningitis is arrested but hydrocephalus results may be expected. This case, therefore, assumes special importance, since it offers an example of a rational method for treating this new complication of meningitis.

The feasibility and, indeed, the desirability of cauterizing the choroid plexus in both lateral ventricles at one session seemed established in those cases in which the hydrocephalus was fulminating. Much valuable time is lost otherwise. Particularly is this true in the case of patients in the wards, where exposure to intercurrent infections, such as colds, purulent otitis media and pneumonia, is a constant threat during the winter months and the possibility of contracting a gastrointestinal disorder with diarrhea is a similar threat during the hot summer months. In several of the earlier cases one or the other of these factors forced long postponement of cauterization of the plexus on the second side, so that the evil effects of the pressure on the cortex continued unrelieved. Of course, in cases in which the pressure is not too excessive the indication for cauterizing both sides at once is less clear and the two stages may profitably be divided.

The mental development of the 9 surviving children of this group may be summarized as follows: Four appear to have normal mentality; 3 appear moderately retarded, and 2 are definitely defective. The patients with a favorable end result constitute 20 per cent of the entire series, or 40 per cent of those in whom the pressure was arrested.

These figures are both discouraging and encouraging. One wishes that the percentage of really satisfying end results were higher. On the other hand, if one analyzes the results in this group carefully a more heartening impression is gained. In the first place, it is evident that the results in the more recent cases are better than in the earlier cases. This is due, in part, to a better selection of patients for operation. In the beginning patients with an advanced stage of hydrocephalus who would not now be accepted were operated on. Today no child is operated on whose head has reached such a size that he would be left conspicuously disfigured should he live. Moreover, today all children have enough air introduced into the ventricles during the preoperative routine study to permit exact determination of the thickness of the cerebral cortex, and if the cortex is so thinned out that there is reasonable doubt that the child could attain average mentality even in the event that the intraventricular pressure were arrested, he is not accepted for operation. Again, in the beginning a conservative cauterization on one side was often done, which resulted in the reduction of intraventricular pressure to a level compatible with life but still left it somewhat above normal. Weeks or months later it might be decided that cauterization of the second side was necessary and could be successfully carried out. During

these intervening months, however, the intraventricular pressure, while not sufficiently high to threaten life, nevertheless was elevated enough to exert a damaging effect on the brain. This was undoubtedly true in cases 3 and 4 in group 3.

Today, in contrast to this approach, the most thorough possible cauterization of the choroid plexus is carried out on both sides at the first operation, which results in the removal at the earliest possible period in the child's life of the damaging effect of slight but protracted pressure on the brain. Finally, aggressive follow-up observation and immediate reoperation if the intraventricular tension does not fall to a normal level after the first operation further minimize the possible damage to the brain by the pressure of the ventricular fluid.

Entire Series of Twenty Cases.—The present study reaffirms the fact that the cerebrospinal fluid is formed by the choroid plexuses within the ventricles of the brain and that destruction of these plexuses will reduce the intraventricular pressure associated with communicating hydrocephalus. Furthermore, it has been demonstrated that in practice the choroid plexuses within the lateral cerebral ventricles can be largely destroyed by means of endoscopic cauterization, with operative death in approximately 15 per cent, without benefit in approximately 35 per cent and with satisfactory reduction of intraventricular fluid pressure to essentially normal levels in approximately 50 per cent of the cases. In 40 per cent of the last group of cases, that is, in 20 per cent of the entire series, normal intellectual development appears to proceed.

These results are in such general agreement with those of Putnam that the two series are mutually corroborative. Earlier diagnosis, wiser selection of patients for treatment and more radical operation offer promise of better results in the future.

SUMMARY

In 1935 I described a new ventriculoscope, which was designed for the treatment of communicating hydrocephalus by cauterization of the choroid plexuses within the lateral cerebral ventricles, and I discussed the technic of its use and made a preliminary report on patients treated with this technic.

The present paper reports my experiences with this instrument and this technic in the treatment of communicating hydrocephalus since that time.

A total of 48 operations have been performed on 20 children. Cauterization of the plexus on one side is herein considered an individual operation. A number of children have also had reoperations performed on the side previously operated on.

Three children died operatively, so that the case mortality was 15 per cent and the operative mortality 6 per cent. There have been no deaths,

however, during the last four years. Seven, or 35 per cent, of the children survived the operation and were discharged from the hospital, but had generally unsatisfactory results. The remaining 10, or 50 per cent, of the children had satisfactory results, in the sense that they attained a lasting reduction of intracranial tension. One of these 10 died after five years; the other 9 are still living, the longest survival period being over six years and the shortest over six months.

Of the 9 children now living, 4 have essentially normal mental development, 3 show moderate retardation and 2 show marked retardation. Those with essentially normal mentality constitute approximately 20 per cent of the entire series operated on, or slightly better than 40 per cent of the surviving group.

A patient with postmeningitic hydrocephalus who was successfully treated is included in the series (case 8, group 3). So far as can be determined, he is the first patient of this sort to be reported on. A second patient who was similarly treated is still living, although the result in his case cannot be considered satisfactory (case 3, group 2).

Acute intraventricular hypotension as a postoperative complication, which occurred in 3 cases, is here described for the first time (case 1, group 1, and cases 2 and 9, group 3), together with methods for treatment.

The importance of early diagnosis, careful choice of patients, radical operation, close follow-up observation and early reoperation if pressure returns has been emphasized and illustrated.

The results warrant a wider use of the principles and methods here presented. Moreover, there is good reason to expect a lower mortality and a higher average mentality in patients so treated in the future.

Case Reports

XANTHOMA OR CHLOROMA

FOLLOW-UP DATA ON CASE OF "CHLOROMA" REPORTED IN 1930

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In September 1941 we had completed fifteen years of follow-up records on a boy whose case was reported by one of us [1] in 1930 as one of chloroma. There have been so many inquiries about this patient that a report of his course to date may not be unwelcome. The very fact of his continued existence has led some to question the accuracy of the original diagnosis. The most commonly suggested alternative has been xanthoma. It seems wise, therefore, to reconsider this entire case in the light of the more recent studies published since 1927, when the original diagnosis of chloroma was made.

REPORT OF PATIENT'S COURSE FROM 1929 TO 1941

Kenneth D., a white boy born Feb. 15, 1925, was admitted first to the University of California Hospital on Sept. 29, 1926. A complete account of his history and of the examinations, treatment and course to May 1929 is contained in the original report.[1] This also includes illustrations of the tumors of the head, femur, tibia and mediastinum together with reproductions of roentgenograms, histologic sections and blood smears. The patient's recovery appeared to be complete in 1929. His course since that date is given in the following text, by years of age, into his seventeenth year of life.

1929-1930, Fifth Year.—The patient enjoyed good health, showed average progress and had no serious illnesses. Except for one attack of "summer diarrhea" he had no complaints. He was seen several times and showed no unusual signs in physical or roentgen examination. The only abnormality in his blood was a mild leukopenia (5,000 to 7,000 white cells per cubic millimeter).

1930-1931, Sixth Year.—Again there were no serious complaints. Information obtained by correspondence and from one visit revealed only a few mild colds.

1931-1932, Seventh Year.—In November 1931 the patient was brought from his home in Corcoran, Calif., to Denver. The year had been a healthy one. Exami-

From the pediatric departments of the School of Medicine of the University of Colorado and the University of California Medical School.

1. Washburn, A. H.: Chloroma: Report of a Case with Recovery Following Roentgenotherapy, with a Review of the Literature, Am. J. Dis. Child. **39**:330-348 (Feb.) 1930.

nation showed a slender but apparently healthy boy. The only abnormal finding noted was a slight difference in the length of the two legs, the right being shorter than the left. Neither roentgenograms nor blood counts revealed anything unusual.

1932-1933, Eighth Year.—Correspondence with Kenneth's mother suggested nothing except normal health and progress during this year.

1933-1934, Ninth Year.—In September 1933 the patient was seen again in Denver. Physical and roentgen examination and blood counts showed no new or unusual findings. He was still rather slender and was said to be "a fussy eater like his father." In January 1934 he was admitted to the University of California Hospital, in San Francisco, with a small tumor posterior to the left ear. This was removed, sectioned, and diagnosed as an "angioendothelioma." The red blood cell count was 4,550,000; the hemoglobin count was 12.5 Gm. per hundred cubic centimeters, and the white cells numbered 5,100, with the differential count normal. In February he had a very severe attack of whooping cough with slow convalescence.

1934-1935, Tenth Year.—In May 1934 Kenneth had a very severe attack of measles. This was followed by months of poor health with pallor, fatigue and a long series of "boils." The winter of 1934-1935 was his least healthy one since that of 1926-1927. He had many "colds," several nosebleeds and an almost constant complaint of being "very tired." Growth seemed slow, and he looked thin and pale when seen briefly in November. Unfortunately, it was not possible to obtain roentgenograms or examinations of the blood at that time.

1935-1936, Eleventh Year.—Though not as bad as in the previous year, his health during this year was not good. He had many colds with several severe attacks of epistaxis, and his recovery each time seemed unduly slow. He seemed frequently fatigued and had a hard time keeping up with his class in school (sixth grade).

1936-1937, Twelfth Year.—In February and March 1936 the patient had a severe attack of influenza complicated by two severe nosebleeds. Progress in school was good in spite of his illness. By July 1936, when he was brought to Denver, he appeared to have made a good recovery. While not a robust lad, he appeared to be in good general health. The roentgenograms showed normal structures except for a short right femur and tibia and a small simple exostosis at the lower end of the shaft of the left tibia. The red blood cell count was 4,724,000; the hemoglobin content was 14.2 Gm. per hundred cubic centimeters and the white cells numbered 5,475, with a normal differential count. The remainder of this year was uneventful.

1937-1938, Thirteenth Year.—This was a very good year. The boy's health was described as "excellent"; he had only a few mild "colds," and he made good progress in school. His only complaint concerned the shortness of his right leg, which was remedied by increasing the height of the lift in his shoe. When he visited Denver in July 1937 he weighed 66 pounds (29.7 Kg.) and was 56½ inches (141 cm.) tall. Though relatively small and slender for his age, he seemed to be in good health. There were no new findings on examination or in the roentgenograms. His red cell count was 4,100,000; the hemoglobin content was 13 Gm. per hundred cubic centimeters, and the white cells numbered 4,300, with a normal differential count. The rest of this year passed without further illnesses.

1938-1939, Fourteenth Year.—During this year Kenneth's growth was slow and his health definitely below average. He showed a tendency to be fussy and slow in eating, had a consistently poor appetite and complained frequently of fatigue.

He was overactive in school and boy scout work, refused to rest during the day and was overanxious to do well. He came to Denver for a day in June 1938. Physical examination revealed no new or significant signs. He was thin but not pale. He was in good spirits and seemed to be in fairly good health. Roentgenograms of the long bones remained unchanged except for growth, and this was slower than the average. Rather complete anthropometric studies showed that he was small and light for his age, his weight being 73 pounds (32.8 Kg.) and his height 59 inches (147 cm.). However, only his leg measurements were actually abnormal, his right leg being nearly 2 inches (5 cm.) shorter than the left. The blood showed

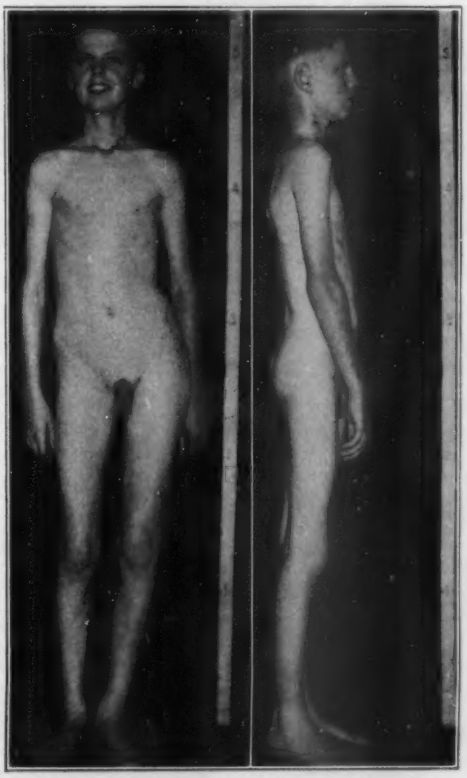

Fig. 1.—The patient, Kenneth D., in June 1940. Note shortening of the right leg. (Tilt of pelvis relieved by lift in shoe.)

4,880,000 red cells, 13.3 Gm. of hemoglobin per hundred cubic centimeter and 6,150 white cells. The only striking deviation from the average was the unusually small mean corpuscular volume, of 69 cubic microns.

1939-1940, Fifteenth Year.—During this winter the patient had a second severe attack of influenza, complicated by a prolonged epistaxis. For several months following this episode, he was said to have been pale and weak and willing to avoid exercise. In spite of this illness he kept up with the work of his class in the ninth grade. Moreover, he showed the first signs of adolescence during this year. He was not seen during this year, but there was correspondence with his mother.

Fig. 2.—Roentgenograms of the head, taken in June 1940.

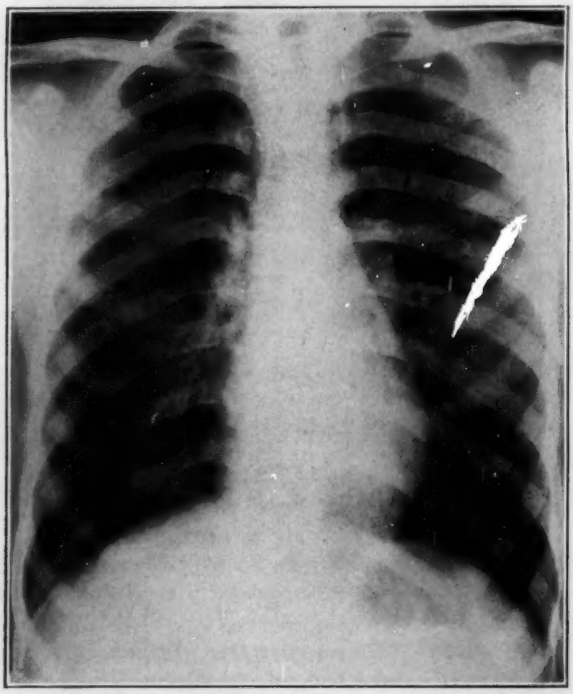

Fig. 3.—Roentgenogram of the chest, taken in June 1940.

1940-1941, Sixteenth Year.—By the summer of 1940 his health was much improved. His family brought him to Denver in June and stayed two days, so that we were able to do a little more careful checking than usual. His weight was 80½ pounds (36.2 Kg.) and his height 62⅜ inches (156 cm.). His general health and morale seemed excellent (fig. 1). Positive physical findings were: a plexus of dilated

Fig. 4.—*A,* Right femur, tibia and fibula as they appeared in June 1940. *B,* Left femur, tibia and fibula as they appeared in June 1940.

superficial veins in his nose (reported as cauterized at a later date); exostosis of the lower end of the left tibia unchanged since the previous visit; and slight retardation of adolescence, which seemed to be at about the stage one would expect in the average boy of 14 years. A very complete roentgenologic study revealed nothing new (figs. 3 to 6). The blood counts were within normal limits, showing red cells

5,240,000, hemoglobin 15 Gm. per hundred cubic centimeters, packed red cells 39.1 per cent, white cells 5,800 and a normal differential count. The blood cholesterol content was 136 mg. per hundred cubic centimeters (normal 120 to 225 mg.). The carbohydrate tolerance curve showed an average form. From the history it was concluded that his diet had been inadequate, particularly in proteins and vitamins. Both Kenneth and his mother were advised accordingly.

September 1941, Age 16½ Years.—Letters from Kenneth and his mother, written early in August 1941, describe this year as an unusually healthy one. He

Fig. 5.—Appearance of bones of the arm in June 1940.

did well in school, missing no time on account of illness during the school year. He was active, eating well and growing faster than before. He weighed 90 pounds (40.5 Kg.) in July 1941. In late August a routine follow-up visit was made to the University of California Hospital. Physical examination and roentgenograms of the skull, chest and extremities revealed nothing new.

Conclusion.—During this entire follow-up record from 1929 to 1941 none of the following symptoms and signs have ever been noted: cutaneous skin lesions and pigmentation suggesting xanthoma; polydipsia, polyuria and other symptoms

suggesting endocrine disturbance; bone defects; exophthalmos; neurologic disturbances, and cardiovascular abnormalities. The moderate degree of retardation in his physical growth and in the onset of adolescence does not place him outside the range of variation to be found in a group of average children. There has never been any noticeable retardation in his mental growth.

Fig. 6.—Hands and feet as they appeared in June 1940.

COMMENT

In 1932 several members of the University of California staff, notably the late Dr. Charles Connor, pathologist, and the late Dr. Alfred Heald, roentgenologist, suggested that this might have been a case of

xanthoma rather than of chloroma. This diagnosis was suggested by a study of Sosman's papers,[2] in which were mentioned several cases in which xanthoma had been diagnosed erroneously as multiple myelomas and one in which it had been called chloroma. In a very complete discussion of xanthoma in Brennemann's "Practice of Pediatrics," Rowland[3] also mentioned the possibility of confusion between xanthoma and chloroma in small children. It cannot be denied that there is at least the possibility that our patient, Kenneth D., may have been suffering from xanthoma rather than from chloroma. Such a diagnosis might offer a more acceptable explanation for his prompt response to roentgen ray treatment and, indeed, for his whole course to date. For this reason we carried out a rather prolonged review, discussion and reconsideration of the whole case in the years 1935 to 1937.

Unfortunately there were two incidents which handicapped this review. A fire in the department of roentgenology had destroyed all the original films, and only the small group of reproductions[1] remained. In addition to this tragedy, the pathology department had undergone a complete reorganization, with refiling and renumbering of specimens. The original stained sections of Kenneth's tumors were not found. Old tissue blocks had been stored, but not always with adequate labels. To quote the report from Dr. Connor's laboratory on Feb. 13, 1934, there were "five blocks obtained from the old storeroom which probably represent the sections taken from the tumor mass." New sections were made from these old blocks. During 1935 and 1936 these were rather widely circulated among a number of pathologists, including members of the Committee on Bone Sarcoma. During the summer of 1936 one of us (A. H. W.) went over all this material in detail with Dr. Connor. Drs. Stuart, Hartman and Morton made definite diagnoses of xanthoma, the last named going so far as to write "good case." Dr. Simmons thought the condition was probably xanthoma, judging from the history. Dr. Crowell said that it might be xanthoma but that he would be unable to make a diagnosis from the sections alone. Dr. Connor was in agreement with Dr. Crowell. Dr. Codman considered the sections "typical of chordoma." Dr. William Johnson thought the tumor definitely myelocytic and judged it to be chloroma on the basis of the original gross description. From a number of other pathologists who saw these

2. Sosman, M. C.: Xanthomatosis (Schüller's Disease; Christian's Syndrome): Report of Three Cases Treated with Roentgen Rays, Am. J. Roentgenol. **23**:581-597 (June) 1930; Xanthomatosis, J. A. M. A. **98**:111-117 (Jan. 9) 1932.

3. Rowland, R. S.: Constitutional Disturbances of Lipid Metabolism, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1937, vol. 3, chap. 23, pp. 15-46.

sections there came diagnoses of xanthoma, chloroma, myeloma, granuloma and sarcoma. With these contradictions in mind we returned to the original data.

One of us (A. H. W.) was present at the operation in which Dr. Naffziger removed the tumor from the head. This gave the appearance of a malignant neoplasm infiltrating the periosteum and largely the outer plate of the skull. The tumor was examined in the gross immediately, and thin fresh sections were squeezed out on slides and then stained and examined as described in the original report.[1] Dr. Washburn took the tumor to the pathology department himself. There Dr. Rusk (then professor of pathology) made fresh sections and took blocks for fixation, staining and microscopic study. Subsequently, on a number of occasions we studied all the tissue sections made from the tumors of the head and of the ears. The evidence thus accumulated may be summarized briefly. The fresh-cut surface of the tumor removed from the head was described as being "green" or "grayish green" by three different observers. The tumors from the ears showed a dirty gray color when sectioned. In most histologic sections studied there was a great preponderance of relatively undifferentiated cells, judged to be myelogenous in the fresh smears stained with Wright's stain, in those stained with the peroxidase stain and in the fixed tissue sections. These cells averaged about 10 microns in diameter, varying from 5 to 15 microns. They not only were smaller than the typical foam cells of a xanthoma but showed larger and more vesicular nuclei and no "foamy" appearance of their cytoplasms. While Dr. Rusk declined to make a diagnosis of chloroma from the microscopic examination of these sections, he did believe that we were dealing with a myelogenous type of tumor. His final decision in favor of calling it chloroma was based on the combined evidence of all the gross and microscopic descriptions. Unfortunately no histochemical staining was done to determine the presence of fats or lipids.

At the present time we feel that a review of all this evidence obtained from the studies of pathologists fails to clinch the diagnosis. The infiltrating character of the tumor, its involvement largely of the outer plate of the skull, the green color on freshly cut surfaces and the results of the various original microscopic studies—all favor a diagnosis of chloroma. The various reports on the reexamination of the new sections —assuming that they were made from one of Kenneth D.'s original tumor blocks—show that about half of all the pathologists consulted favored the diagnosis of xanthoma.

Being unable to reach a definite decision on the basis of the pathologic studies, we turned to a review of the whole clinical picture. In the

history obtained at the time of his first admission, Kenneth's parents stated that they noted the swelling first at the age of 10 months, that it almost disappeared during the interval from 15 to 18 months and that it grew rapidly and steadily thereafter. Assuming these observations to have been reliable, such a course might be more consistent with the diagnosis of xanthoma. The patient's appearance at the time of his first admission was consistent with either diagnosis, but it was believed by one of us (A. H. W.) to favor that of chloroma. The grayish pallor of his face, particularly of the skin overlying the tumor mass, may have been responsible for this impression. The child was well developed and well nourished but showed the sort of pallor and facies which one associates with an acute leukemia at this age. Frequently repeated blood counts during the first eight to ten months of his course showed 50 to 80 per cent of his white blood cells to be of the myelogenous series, well over half of these being usually immature forms.[1] The picture was similar to that which we have observed in so-called "aleukemic leukemia." The blood picture seems to be definitely more consistent with chloroma than with xanthoma.

Any one, of course, will grant that the mere survival of the patient gives more support to a diagnosis of xanthoma.[4] However, a careful review of his history during the fifteen years which have elapsed since the start of his roentgen ray treatments in December 1926 makes it quite apparent that while such a course is unheard of in a small child with chloroma, it is at least almost as surprising in a small child with such widespread xanthomatosis. That is, the lack of any recurrence or relapse during treatment and the complete absence of any specific symptoms of the disease for the subsequent fifteen years would stamp this case as a very unusual instance of xanthoma. It is true, no doubt, that one might be justified in arguing that the relatively slow growth and physical development, lack of optimum nutrition and susceptibility to infection are all symptoms consistent with a diagnosis of xanthoma. There are, however, other factors which account for this picture more easily. His father and mother are both very slender, and his father is a relatively small man and a poor eater. The boy's own diet has been inadequate, and both he and his parents have been, at times, over-

4. The last review of the literature, by Kandel[5] in 1937 (Kandel, E. V.: Chloroma: Review of the Literature from 1926 to 1936 and Report of Three Cases, Arch. Int. Med. **59**:691-704 [April] 1937), brought the total number of cases of chloroma to 175. A brief review of the literature from 1936 through the year 1940 yielded 30 additional reported cases. No recoveries have been reported since 1930. In contrast to this, the extensive literature which has been accumulating on xanthoma of the Hand-Schüller-Christian type contains many reports of remarkable relief following roentgenotherapy.

solicitous about his health. Finally, with attention to some of these difficulties during the last two years he has shown a good deal of improvement in his general health.

There remains only the reconsideration of the roentgenograms, in which we have been handicapped by the loss of the original films. In the original roentgenograms, covering all the bones of the body and the pulmonary fields as well, the following lesions were demonstrated: one tumor of the skull involving destruction of the outer plate in the left frontal region, one tumor of the right femur with both destruction and production of bone, one small area in the right tibia showing mostly destruction, and a mediastinal tumor in the supracardiac region which appeared to be about half the size of the heart. The lesion of the skull not only was a single lesion but showed nothing of the typical "punched-out" or "maplike" appearance usually seen in cases of xanthoma. When

Strength of Evidence in Differential Diagnosis

Symptoms or Signs	Chloroma	Xanthoma
Initial history	+	+++
Initial physical examination	+++	++
All roentgenograms	++	++
All blood counts	++	+
Gross appearance of tumor	+++	+
Microscopic examination, 1926	+++	
Microscopic examination, 1936	+	+++
Clinical course	....	+++
Total number plus signs	15	15

this healed it left a depression, which can still be located by palpation. Although the lesions of the femur and tibia did not appear to involve the epiphyses and although they healed completely, as far as one could judge from the roentgenograms, there has been slower growth of these bones than of the corresponding bones on the left side. There has never been any evidence observed of further involvement of the bony skeleton during the fifteen years of our follow-up record.

From all this discussion it must be apparent that there is no one piece of incontrovertible evidence which enables us to say with confidence that this patient had either xanthoma or chloroma. We have tried to summarize the strength of the evidence for each diagnosis in the accompanying table, admitting that the selection and weighing of items are arbitrary.

One of us (A. H. W.) is inclined to diagnose the condition as an atypical myelogenous tumor, most satisfactorily classified as a chloroma. It is, however, obvious that no matter how one weighs the available evidence the final diagnosis remains in doubt. For this reason we prefer to leave the question of final diagnosis open until such time as further knowledge of these diseases or of this patient settles the issue.

OSTEITIS TUBERCULOSA MULTIPLEX CYSTOIDES IN CHILDREN

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AND
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Cystic tuberculosis of bone is an uncommon form of osseous tuberculosis which rarely occurs in children. Heretofore only 14 such cases have been reported.

Jüngling [1] in 1920 first reported on this disease and termed it osteitis tuberculosa multiplex cystica. Reviewing the subject in 1928, he found 55 cases, including 9 of his own. All of the patients were adults. These collected cases had the following characteristics: (1) The onset was gradual; (2) pain began early but was not severe; (3) the onset occurred during puberty or thereafter; (4) the small long bones of the hands and feet were most often affected; (5) there was a tendency to formation of large cysts without surrounding sclerosis; (6) there was no involvement of the periosteum or the joints; (7) the tuberculin test usually gave negative results; (8) tubercle bacilli were not found by stains, cultures or guinea pig inoculation; (9) microscopic examination showed epithelioid cells, rarely giant cells, and no caseation; (10) there were often associated lesions of the skin (sarcoid); (11) the course was slow, with a tendency to improvement; (12) the patient's general health usually was unimpaired.

Cases in which the disease occurred in children were later discovered. Law and Perham [2] in 1938 collected 10 such cases and added one of their own to the literature. Since that date there have been single case reports by Martin,[3] and Lovett and Wolbach,[4] writing in 1920 on tuberculous disease of the bones, included 2 cases of a condition that

From the departments of pediatrics of the Cumberland and the Swedish Hospital.

1. Jüngling, O.: Fortschr. a. d. Geb. d. Röntgenstrahlen **27**:357, 1920; Beitr. z. klin. Chir. **143**:401, 1928.

2. Law, J. L., and Perham, W. S.: Multiple Cystic Tuberculosis of Bones in Children, Am. J. Dis. Child. **56**:831 (Oct.) 1938.

3. Martin, D. W.: J. Pediat. **15**:254, 1939. Martin, D. W., and Fogel, D. H.: Multiple Cystic Tuberculosis of Bones, Am. J. Dis. Child. **61**:322 (Feb.) 1941.

4. Lovett, R. W., and Wolbach, S. B.: Surg., Gynec. & Obst. **31**:111, 1920.

fits well into the category of tuberculous cystic disease which should be added to the aforementioned list.

The reported cases of this disease in children differ from Jüngling's case (adult patients) in that: (1) there was a greater tendency to involvement of long hollow bones; (2) associated cutaneous skin lesions were infrequently encountered (in 72 per cent of the cases in Jüngling's series there were associated cutaneous lesions); (3) tuberculin tests usually gave markedly positive results; (4) guinea pig inoculations sometimes gave positive results; (5) caseation was occasionally noted; (6) there was a tendency for the lesions to heal locally, but frequently the patient died of generalized tuberculosis shortly after they were healed.

It appears to us that the condition in the cases reported by Jüngling resembles Boeck's sarcoid and that the osteitis tuberculosa multiplex cystica that occurs in children represents an entity which is intermediate between Boeck's sarcoid and caseous tuberculosis of bone.

PATHOLOGY

From a focus elsewhere in the body (in children usually the mediastinal lymphoglandular structure) tubercle bacilli are carried by the blood stream to the bone marrow. As the bacilli multiply and grow, typical tuberculous follicles with lymphocytes, epithelioid cells and giant cells form. These coalesce, and caseation begins at the center while fibrosis goes on at the periphery. In most cases caseation is more rapid than fibrosis and the process infiltrates the surrounding tissues, with subsequent epiphysial destruction, articular involvement and abscess and sinus formation.

Rarely the fibrotic reaction predominates over the caseative and a circumscribed area of soft granulation tissue and degenerated bone is formed. No definite capsule can be made out. This is the lesion described as osteitis tuberculosa cystica. "Cystica" describes the roentgenographic picture, for only after curettement is the lesion converted into a cystlike cavity (Jüngling later used the term "cystoides"). The process may remain unchanged for long periods, may progress to abscess formation or may retrogress to almost complete healing. In osseous tuberculosis, when the caseation begins early the progressive type is most apt to occur. For this reason the stationary or retrogressive lesion is uncommon, and this probably explains the paucity of cases of cystic tuberculosis of bone.

REPORT OF A CASE

E. F., a Negro boy aged 16 months, was admitted to the Swedish Hospital on Aug. 20, 1940, with a history of having been struck on the head with a piece of

plaster falling from the ceiling the day before admission. Next day a large lump was noted in the right frontal and orbital regions.

The patient's father died at the age of 35 years (cause unknown). The mother was well, and roentgen examination of her chest failed to reveal tuberculosis. She said she had not had any venereal disease.

The patient was delivered spontaneously, weighing 8½ pounds (3,856 Gm.). There were no postnatal complications. He had his first tooth at 7 months and walked and talked at 1 year. He had been given 1 teaspoon of cod liver oil and 4 ounces (120 cc.) of orange juice daily and had had no feeding difficulties. He had been well except for occasional coryza.

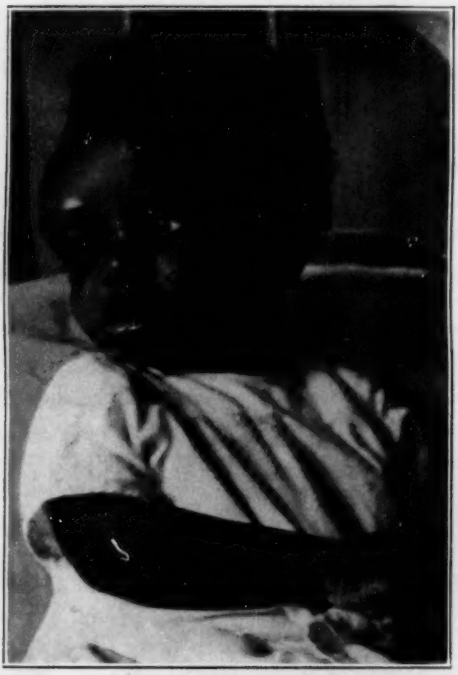

Fig. 1.—Appearance of the patient on admission to the Swedish Hospital.

Physical examination revealed a thin child not appearing acutely ill. A mass about the size of a lemon was felt just above the right supraorbital ridge. The lateral half seemed fluctuant, and the medial half was bony hard, as though the frontal bone was elevated at that point.

The pupils were equal and round and reacted to light. The upper lid of the right eye was markedly swollen and continuous with the mass on the forehead. The right lower lid was also somewhat swollen. The ears, nose and throat were essentially normal.

The lungs were clear and resonant. Breath sounds were normal; there were no rales, and the respiratory excursions were equal.

The heart had a normal rate. It was not found displaced on palpation or percussion. The sounds were of good quality, and there were no murmurs.

The abdomen was soft, with no masses, tenderness or rigidity. The liver, spleen and kidneys were not palpable.

The extremities showed no deformity or limitation of movement.

Neurologic examination revealed nothing abnormal.

The genitalia were those of a normal male infant.

Roentgen examination of the right orbital region showed a sclerosing area with central rarefaction about the orbit. Roentgen examination of the left humerus showed two small areas of rarefaction in its upper third. Biopsy specimens were taken from both these areas on August 23. The report was supraorbital tumor and areas resembling caseous necrosis with many Langhans type giant cells and polynuclear, round and plasma cells. The left humerus also showed granulation tissue with multinucleated giant cells surrounded by epithelioid and round cells. An occasional area of caseation necrosis was seen. Special stains failed to disclose any tubercle bacilli.

The mass gradually became smaller, and the orbital swelling receded. On October 22 the child was transferred to Cumberland Hospital for further study.

Physical examination at that time revealed nothing new except for a granulating wound over the right frontal area. Pressure around this region caused exudation of greenish purulent material. There was still some swelling of the right eyelid.

The hemoglobin content of the blood was 8.6 Gm. per hundred cubic centimeters; the red cells numbered 4,400,000 and the white cells 24,000, with 54 per cent polymorphonuclear leukocytes, 2 per cent eosinophils and 44 per cent lymphocytes. Urinalyses repeatedly gave negative results except for showing an occasional trace of albumin. Urine, stools and gastric washings repeatedly failed to show tubercle bacilli, as did three smears from the ulcerated area on the scalp. The urine was not found to contain Bence Jones proteose. The following values were obtained in chemical examination of the blood: sugar, 111 mg. per hundred cubic centimeters, calcium 11.0 mg., phosphorus 6.4 mg., phosphatase 6.4 Bodansky units, urea nitrogen 13 mg., uric acid 2.8 mg., albumin 3.72 Gm. and globulin 4.1 Gm. The sedimentation rate was 24 mm. in one hour. The Wassermann reaction of the blood was negative. The Kahn reaction of the mother's blood was negative. The Mantoux test with a 1:10,000 dilution of old tuberculin elicited a 4 plus reaction with slough formation. The spinal fluid was normal, with a negative Wassermann reaction. The Weltmann band was 9. Guinea pig inoculation failed to produce tuberculosis. Culture of purulent material from the frontal area revealed nonhemolytic streptococci.

Dr. H. Koiransky reported on the roentgenograms as follows:

Chest: "Very marked widening of the mediastinal shadow is seen. The borders of this shadow are crenated, especially on the right side. This is most probably due to enlarged lymphoglandular structures. In the lateral exposure the trachea is poorly visualized, somewhat encroached on."

Skull: "A circumscribed bone defect is noted in the right frontal region above the right orbit and close to the temporal plane. Another area of rarefaction is noted in the left occipitoparietal region."

Left Humerus: "Two sharply punched-out circumscribed bone defects are noted in the upper third of the left humerus. The much more marked visualization and sharp definition can most probably be explained by the previous surgical intervention for biopsy purposes."

The temperature ranged from 98 to 104 F. with afebrile periods as long as two weeks. The pulse was usually rapid, the rate ranging from 92 to 160 per minute.

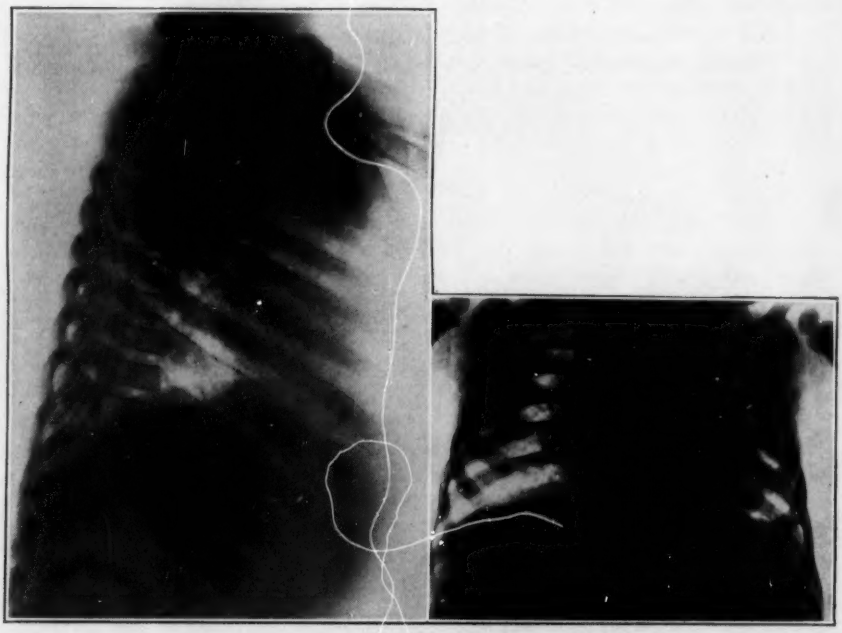

Fig. 2.—Roentgenograms of the chest, showing marked widening of the upper mediastinal shadow and crenated borders, the latter probably due to enlarged lymphoglandular structures.

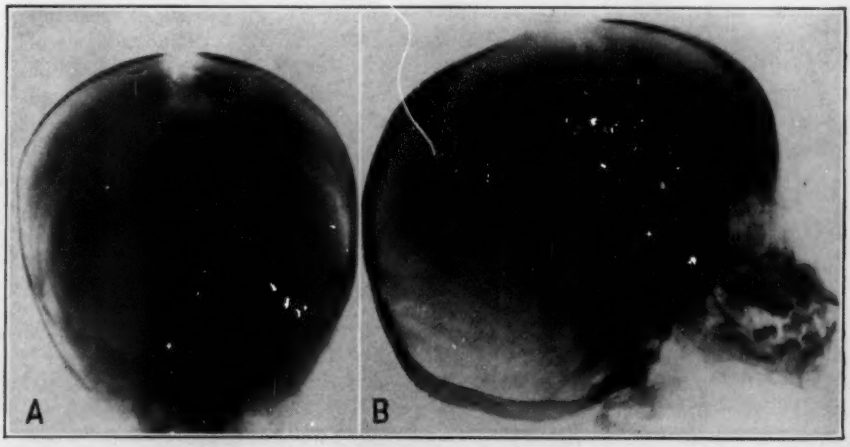

Fig. 3.—Roentgenograms of the skull. *A* shows a circumscribed bone defect in the right frontal region; *B*, an area of rarefaction in the left occipitoparietal region.

The respiratory rate varied from 20 to 60 per minute. Biopsy of scalp and skull tissue on Jan. 15, 1941 by Dr. S. H. Polayes revealed the following picture:

"Giant cell tubercles and epithelioid, round and plasma cells are present. The osseous tissue shows necrosis with dense fibrosis between the trabeculae of bone. Stain for tubercle bacilli gave negative results. The diagnosis is: (1) tuberculous inflammation of skin and bone, (2) osseous necrosis."

On Jan. 26, 1941 bilateral acute purulent otitis media developed. The discharge on culture revealed Staphylococcus albus and Bacillus diphtheroides. Sulfanilamide therapy was instituted. The discharge from the left ear receded, but the right ear continued to discharge a moderate amount of purulent material. On March 18

Fig. 4.—Roentgenogram of the left humerus, showing two sharply punched-out, circumscribed bone defects in its upper third.

mastoiditis with retroauricular swelling developed on the right side. Treatment with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) was instituted preoperatively, and on March 20 the patient underwent a simple mastoidectomy. Sulfathiazole therapy was continued. Four days postoperatively the child had a maculopapular rash on his face, body and extremities and a temperature of 104 F. About two weeks previously he had been exposed to measles and had received 5 cc. of convalescent serum on the day of exposure. There were no Koplik spots, and the rash was more papular than macular. The administration of sulfathiazole was stopped, and the rash and temperature both promptly receded. The mastoidectomy wound continued to drain. A culture of exudate from the mastoid region failed to

yield tubercle bacilli and, in fact, was sterile. Here again, on microscopic examination numerous giant cells and irregularly distributed areas of abscess formation throughout the inflammatory tissue were noted. The diagnosis was:

"Suppurative inflammation (probably tuberculous)." At about this time a marked kyphosis developed in the upper dorsal region. Roentgen examination

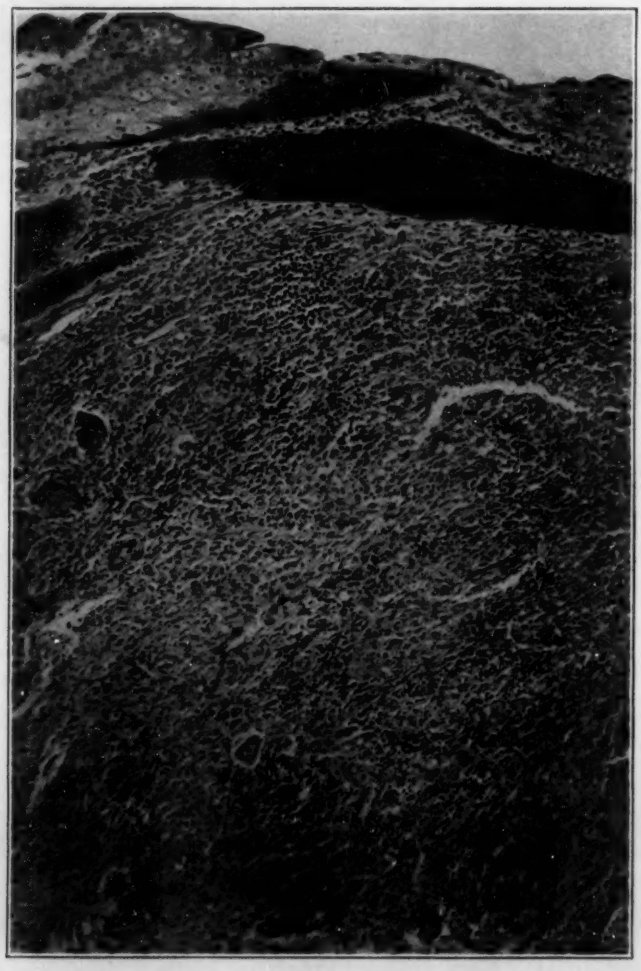

Fig. 5.—Section of scalp and skull tissue, showing giant cell tubercles and epithelioid, round and plasma cells.

showed that the fourth dorsal vertebra was completely destroyed and slipped posteriorly. Also, the third and fifth thoracic vertebrae were markedly eroded. In view of the previous evidence of osteitis tuberculosa multiplex cystoides, these lesions were most probably tuberculous in origin. No pathologic neurologic signs suggesting compression of the cord were noted. The child was put on a Bradford

frame and transferred to the Swedish Hospital for further orthopedic care. The right frontal and mastoid areas continued to discharge. Roentgen examination of the chest, skull, humerus and vertebrae showed no appreciable changes since admission.

The clinical diagnosis was (1) osteitis tuberculosa multiplex cystoides, (2) mediastinal lymphoglandular tuberculosis, (3) mastoiditis (right side) and (4) Pott's disease.

SUMMARY

The case reported demonstrates the symptoms, signs and histologic and roentgenologic changes in a relatively rare tuberculous infection of bone, best termed osteitis tuberculosa multiplex cystoides. It must be differentiated from syphilis, nonspecific osteomyelitis, multiple myeloma, osteitis fibrosa cystica, Hand-Schüller-Christian disease, Gaucher's disease, echinococcic cysts, coccidiosis, leprosy, giant cell sarcoma and metastatic malignant growth.

MYASTHENIA GRAVIS

REPORT OF ITS OCCURRENCE IN A TWENTY-ONE MONTH OLD INFANT

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PAUL K. ITO, M.D.
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Myasthenia gravis is a rather uncommon disease in infancy and childhood. The first report of its occurrence in a child was given by Remak [1] in 1892. The patient was a girl 12 years of age. In April 1941, Levethan, Fried and Madonick [2] were able to collect 34 cases from the literature in which the age of the patient was under 17 years. Only 8 patients were under 10 years of age. The youngest mentioned in the literature was an infant of 23 months, reported on by Booth [3] in 1908. Our patient being an infant of 21 months, the case seems worth reporting.

REPORT OF A CASE

T. K., a boy aged 21 months, born in Los Angeles of Oriental parentage, was first brought in for examination on Aug. 12, 1940. The chief complaint was drooping of the eyelids for one month.

History of Present Complaint.—About July 10, 1940, the mother noticed the drooping of the left eyelid. This continued for about a week; then both eyes seemed to be involved. At first the symptom was noticed only off and on and was thought to be definitely better in the morning, with increasing prominence as the day progressed. The face had a somewhat ironed-out appearance.

Past History.—The patient had had none of the childhood diseases. He was a full term baby and was born spontaneously, weighing 6 pounds (2,722 Gm.) at birth. He was breast fed; he had his first tooth at 9 months and began to walk at 18 months. There had been no operations. The patient had received an injury to the forehead, apparently through a bump, but this had no definite residuals. No other injuries and no broken bones were reported. The patient had fourteen hours of sleep a day; he had adequate exercise and ate ample vegetables and fruits during

1. Remak, E.: Zur Pathologie der Bulbärparalyse, Arch. f. Psychiat. **23**:919, 1892.

2. Levethan, S. T.; Fried, A. J., and Madonick, M. J.: Myasthenia Gravis: Report of Case in Which Prostigmine Methylsulfate Was Used, Am. J. Dis. Child. **61**:770 (April) 1941.

3. Booth, J. A.: Report of a Case of Myasthenia Gravis Pseudoparalytica with Negative Pathological Findings, J. Nerv. & Ment. Dis. **35**:690, 1908.

the day. He drank 3 pints of milk (1.4 liters) and 2 to 3 pints (0.9 to 1.4 liters) of water daily. The patient being an infant, some of the other history data did not apply.

Symptoms Referable to the Systems.—There was no complaint involving any of the various systems other than the trouble with the eyelids and a possible difficulty in speech, since the infant had not learned to talk as yet.

Family History.—The patient's father and mother were living; their ages were 25 and 23 years, respectively. The mother had no history of venereal diseases or miscarriages. There were no other children. No history of hereditary or transmissible diseases in the family was found. No history of any nervous disorder or disease of the brain, spinal cord or nerves in the family was reported.

Examination.—Present Status: The patient was a well developed and well nourished Oriental boy of 21 months who was conscious and rational, active and alert, but who presented an obvious drooping of both eyelids and a definite ironing-out of the face, with loss of expression.

Head: Examination of the head failed to show any evidence of increased intracranial pressure, and no local swellings of the scalp or skull were evident. Aside from the drooping of the eyelids there was nothing unusual about the eyes, nose or throat. There was some drooping of the face, so that the infant appeared rather expressionless.

During the course of the examination the infant began to cry, and it seemed that all signs promptly became definitely worse. The left lid drooped excessively, and the infant was unable to raise his lids at all without a definite and obvious overaction of the frontal muscles in an attempt to compensate for the weakness of the levators. The face during the crying spell was entirely ironed out, only the lower lip taking any part in the movement. The mouth drooped open, its corners being depressed.

Neck: There was no stiffness of the neck.

Thorax: Examination of the chest showed no evident disease of the heart or lungs.

Abdomen: No enlarged organs or tumor masses were palpated. No striations, scars or herniations were noted.

Genitalia: Examination of the external genitalia gave negative results.

Extremities: The extremities showed no deformity, atrophy or paralysis.

Cranial Nerves: Because of the infant's age, no definite or adequate examination could be made of the special senses, but there was no reason to believe that there was any disturbance of the sense of smell, taste, sight or hearing. Examination showed the optic fundi to be perfectly normal, the disk being sharp and the cups present and the vessels not being unusually engorged or tortuous. There was an obvious drooping of both eyelids, which at the time of the examination was more noticeable on the left than on the right. There was no other weakness of the extraocular muscles. There were no disturbances of sensation in the face, and the masseter muscles were apparently normal. There was, however, a definite grouping of the musculature of the face, which produced an ironing-out of the nasolabial folds, so that the infant cried essentially with his chin. Examination of the throat showed no definite weakness of the palatal fold, but the palatal reflexes were perhaps slightly diminished. No history of dysarthria or dysphagia was reported. There was no weakness of the musculature supplied by the eleventh and twelfth cranial nerves.

Psychic Functions: The infant had apparently developed normally in the psychic fields, as far as could be observed.

Motor Symptoms: The motor symptoms were confined essentially to the muscles supplied by the third and seventh cranial nerves, namely, the superior levators (responsible for the drooping of the eyelids) and the musculature of the entire face.

Sensory Symptoms: On examination, all senses were found to be intact and equally impressionable on the right and the left side. All of the special senses (smell, taste, sight and hearing) were intact, and there was no history of hallucinations or of impairment of any sense.

Autonomic Function: There were no subjective complaints or any objective evidence to indicate a disorder of the autonomic nervous system in either its central or its peripheral components.

Trophic Disturbances: No trophic changes were noted in the skin, muscles, bones or joints.

Apraxia, Agnosia and Aphasia: No subjective or objective indications of these disturbances were evident.

Reflexes: The deep reflexes, both right and left, were very active, and no pathologic reflexes were in evidence.

Laboratory Findings.—Wassermann and Kahn tests of the blood were negative. The hemoglobin content was 80 per cent (14 Gm. per hundred cubic centimeters). A blood count showed red cells 4,300,000 and white cells 8,450, with lymphocytes 74 per cent, neutrophils 22 per cent, monocytes 3 per cent and eosinophils 1 per cent. The color index was 0.92. The findings in a urinalysis were essentially negative.

A test with prostigmine methylsulfate was done according to the technic of Schwab and Viets,[4] and the result was found to be definitely positive.

Treatment and Course: The patient was given a vitamin E concentrate (alpha tocopherol) orally. A dose of 30 mg. was given daily.

After a month of this treatment, the patient improved slightly. The treatment was continued, and considerable improvement resulted.

SUMMARY

A case of myasthenia gravis in a 21 month old infant is reported.

112 North San Pedro Street.

4. Schwab, R. S., and Viets, H. R.: The Prostigmin Test in Myasthenia Gravis: Third Report, New England J. Med. **219**:226, 1938.

ECTODERMAL DYSPLASIA OF THE ANHIDROTIC TYPE

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AND
ELMER L. GRIMES, M.D.
PHILADELPHIA

Before McKee and Andrews [1] summarized the condition in 1924, little was known about ectodermal dysplasia of the anhidrotic type. Since then, more cases have been reported,[2] over 30 in all. The diagnosis is not difficult when the condition is fully developed, and the term ectodermal dysplasia has not been applied when the defects occur singly.

To evaluate a given case fully, one must be familiar with the organs or tissues that are derived from the primitive ectoderm. They are as follows:[3] (1) the nervous system, including the adrenal medulla; (2) the epidermis; (3) the lining cells of the sebaceous, sudoriferous and mammary glands; (4) the hair and the nails; (5) the epithelium lining

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From the Philadelphia General Hospital, Department of Pediatrics, service of Dr. Harry Lowenburg Sr.

1. McKee, G. M., and Andrews, G. C.: Congenital Ectodermal Defect, Arch. Dermat. & Syph. **10**:673 (Dec.) 1924.

2. Smith, J.: Hereditary Ectodermal Dysplasia, Arch. Dis. Childhood **4**:215 (Aug.) 1929. Kerley, C. G.: Hereditary Ectodermal Dysplasia in a Boy Fifteen Months of Age, Arch. Pediat. **47**:639 (Oct.) 1930. Gordon, W. H., and Jamieson, R. C.: Ectodermal Dysplasia of the Anhidrotic Type, Ann. Int. Med. **5**:358 (Sept.) 1931. Greene, D., and Abramson, H.: Hereditary Ectodermal Dysplasia, Am. J. Dis. Child. **42**:1401 (Dec.) 1931. Zeligs, M.: Hereditary Ectodermal Dysplasia, Anhidrotic Type, ibid. **44**:394 (Aug.) 1932. Hill, A. M.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type, Arch. Dermat. & Syph. **28**:66 (July) 1933. Hiebert, J. M., and Garland, J.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type, New England J. Med. **210**:784 (April 12) 1934. Thannhauser, S. T.: Ectodermal Dysplasia of the Anhydrotic Type, J. A. M. A. **106**: 908 (March 14) 1936. Lord, L. W., and Wolfe, W. D.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type, Arch. Dermat. & Syph. **38**:893 (Dec.) 1938. Clouston, H. R.: The Major Forms of Hereditary Ectodermal Dysplasia (with Autopsy and Biopsies on the Anhidrotic Type), Canad. M. A. J. **40**:1 (Jan.) 1939. de Silva, P. C. C.: Hereditary Ectodermal Dysplasia of the Anhydrotic Type, Quart. J. Med. **8**:97 (April) 1939. Friedman, R.: Hereditary Ectodermal Dysplasia of the Anhidrotic Type, Urol. & Cutan. Rev. **44**:464 (July) 1940. Goeckermann, W. H.: Congenital Ectodermal Defect, with Report of a Case, Arch. Dermat. & Syph. **1**:396 (April) 1920.

3. Gray, H.: Anatomy of the Human Body, ed. 21, Philadelphia, Lea & Febiger, 1924.

the nose, adjacent air sinuses, cheeks and roof of the mouth and also the epithelium of the cornea, conjunctivas and lacrimal glands; (6) the enamel of the teeth; (7) the anterior lobe of the pituitary gland, and (8) the neuroepithelium of the sense organs.

Symptoms resulting from defects in these organs or tissues, for the most part, are obvious. The most frequent initial symptom observed by the physician is an unexplained extreme hyperpyrexia. This obviously is a result of a defect of the lining epithelium of the sudoriferous glands with consequent absence of sweating. It occurs more commonly in summer, but may occur in winter from wearing of too heavy clothing. The patients also exhibit absence of tears and eyelashes and sparsity and thinning of the hair. There is noted a marked delay in or complete absence of teething. Any teeth that do appear usually decay and fall out prematurely. The skin is hypersensitive, rashes develop easily and it frequently becomes pigmented. This often leads to an erroneous diagnosis of congenital syphilis. Because of the defects of the lining epithelium of the respiratory passages, the patients are subject to frequent and usually severe infections of the respiratory tract, which often are associated with unusually high fever. Other symptoms are deformities of the ears and abnormal formations of the nails. Mental deficiency occurs in some cases.

The main pathologic change is absence of eccrine (sweat) glands in most cases, as in the case described here. Sunderman [4] reported that in his cases the apocrine glands were highly developed, though the involuntary muscles around them were hypoplastic. Roentgen examination of the jaw usually reveals a partial or complete absence of tooth buds (fig. 3). A high sugar tolerance has been observed.[5]

The condition is usually referred to as hereditary, but the existence of positive family histories is not nearly as clearcut as with the hidrotic type. Consequently there are two schools of thought concerning the etiology. Because of the similarity of this type of ectodermal dysplasia in certain respects to congenital syphilis, it was thought by some that ectodermal defects were a complication of the latter disease. This theory was never confirmed, and the question of etiology is concerned with the hereditary nature of the disease as against an individual variation of mutation. It is of interest to examine both sides of the question.

If one assumes that the disease is not hereditary, the cause remains a matter of speculation. Endocrine studies are of no help. Associated endocrine disturbances are consequential rather than causative. These

4. Sunderman, F. W.: Persons Lacking Sweat Glands: Hereditary Ectodermal Dysplasia of the Anhydrotic Type, Arch. Int. Med. **67**:846 (April) 1941.

5. Capper, A., and Bekir, N. M.: Congenital Ectodermal Defect, Arch. Pediat. **54**:160 (March) 1937.

consist of symptoms resulting from failure of the thyrotropic or adrenotropic hormones of the anterior lobe of the pituitary gland. There are those who believe that the cause is an injury occurring around the third month of gestation.[6] The exact picture which the disease presents therefore depends, in part at least, on the developmental stage which may be affected by the injury. The varying picture which may ensue can best be visualized by noting Prentiss and Arey's [7] observations on embryonal development. They expressed the belief that the hair of the scalp, face and eyebrows begins to appear in the second month of gestation. About this time the enamel of the teeth starts to form, by invagination of the ectoderm. The remainder of the tooth begins to develop during the third month of gestation. The body hair appears about the fourth month. The sebaceous glands appear at the same time as the hair in different parts of the body. The anlage of the nervous system becomes distinct from the cutaneous ectoderm very early in gestation, and this would account for the fact that most of these patients are normal mentally and present no nervous disorders. This would also explain why the anterior lobe of the pituitary gland is so seldom involved.

This speculation about injury at the third month of gestation loses significance in the face of slowly rising evidence in the literature that ectodermal dysplasia of the anhidrotic type bears an important relation to hereditary factors. At the present time a summary of the literature points to several instances of positive family histories.[8]

The impression today is that there is a gene mutation in the X chromosome which is sex linked but not completely recessive. Levit [8c] has claimed that it may be conditionally dominant in some families, so that heterozygous females might have the dysplasia but in a milder form. Weech's [8b] idea is that all the cases do not go back to one individual, but that there may occur mutations in the genes of any particular individual regardless of sex. Thus both sexes may be affected. Thereafter the transmission would be sex linked and the anomalies

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6. Andrews, G. C.: Diseases of the Skin, for Practitioners and Students, ed. 2, Philadelphia, W. B. Saunders Company, 1938. Brings, L.: On the Genesis of Congenital Cutaneous Defects, Arch. f. Gynäk. **159**:449, 1935.

7. Prentiss, C. M., and Arey, L. B.: Laboratory Manual and Textbook of Embryology, ed. 3, Philadelphia, W. B. Saunders Company, 1920.

8. (*a*) Clarke, R. E., and McCame, R. A.: Familial Sex-Linked Ectodermal Dysplasia with Incomplete Forms, Arch. Dis. Childhood **9**:39 (Feb.) 1934. (*b*) Weech, A. A.: Hereditary Ectodermal Dysplasia, Am. J. Dis. Child. **37**:766 (April) 1929. (*c*) Levit, S. G.: Problem of Dominance in Man, J. Genetics **33**:411, 1936. (*d*) Hardwick, C.: Two Families Showing Hereditary Ectodermal Dystrophies, Brit. J. Dermat. **51**:24 (Jan.) 1939. (*e*) Brain, R. T.: Ectodermal Defect, Proc. Roy. Soc. Med. **31**:69 (Dec.) 1937.

appear only in the male. Weech believes that this explains the occasional occurrence of the condition in females.

REPORT OF A CASE

P. S., a white boy of 17 months, was admitted to the pediatric service of Dr. Harry Lowenburg Sr. on July 20, 1940.

Family History.—The parents were living and well and showed no abnormalities. They had no other children. There was no history of hereditary or chronic diseases on the maternal side. The mother could recall no congenital abnormalities in her relatives. The father's history was not available.

Past Medical History.—The patient was delivered spontaneously at full term, after a four hour labor period, weighing 8 pounds and 2 ounces (3,685 Gm.). He was breast fed for seven weeks and received adequate amounts of orange juice and cod liver oil. When he was 7 weeks old he had abscesses of both shoulders, for which he was hospitalized four months. At the age of 14 months he had the "left mastoid drained and double pneumonia." At 15 months he was admitted to another hospital for "mastoid trouble," and on June 16, 1940 he was transferred to the Philadelphia Hospital for Contagious Diseases with a diagnosis of measles.

Present Illness.—Five days before his admission to the Philadelphia General Hospital the infant was discharged from the Philadelphia Hospital for Contagious Diseases after his recovery from measles. There was a slight amount of purulent drainage from his left ear. Twenty-four hours before admission the patient had a high fever for no apparent reason. At that time he had a slight rash on his buttocks, which later spread all over his body. Otherwise he was symptom free.

Physical Examination on Admission.—The infant was poorly nourished and appeared younger than his stated age. He was acutely ill, with a rectal temperature of 106 F. His weight on admission was 23 pounds 2 ounces (10,489.30 Gm.).

Red blotches were present on the skin of the face and scalp. The remainder of the body was covered with a diffuse maculopapular eruption. The skin was hot and dry, and there was no evidence of perspiration. (The official temperature in Philadelphia on the day of the examination was 96 F.)

The head showed large frontal bosses and prominent supraorbital ridges. Hypertelorism was present to a moderate degree. The bridge of the nose was markedly depressed, giving a typical saddle-shaped appearance.

The scalp was covered with a short fine fuzz. There were neither eyebrows nor eyelashes.

There was a moderate amount of conjunctivitis, and no tears were noted when the child cried. The scleras were clear, and the irises were blue.

There was no tenderness over the mastoid. The left tympanic membrane appeared thickened and moist, but no perforations were seen. The right tympanic membrane revealed diffuse injection, with some bulging of Shrapnell's membrane.

The nose was saddle shaped. The mucous membrane was pale and dry, and there were many crusts.

The tongue was moist and coated. The pharynx was moderately injected, and the tonsils were large, cryptic and injected. The patient had no teeth.

Rigidity of the neck was not noted. A few small cervical lymph glands were palpable. The thyroid gland was not palpable.

The spine had normal curvature and mobility, and tenderness was not noted.

The thorax was symmetric, with expansion equal on the two sides. Respirations were normal.

The lungs were normal to palpation, percussion and auscultation.

The heart had regular sinus rhythm, with the rate rapid. There was no enlargement to percussion, and no murmurs were noted.

Fig. 1.—Photograph of the patient, showing malnutrition, fine fuzz on the scalp, absence of eyebrows and a saddle-shaped nasal bridge.

The abdomen was scaphoid. The edge of the liver was felt at the costal margin. The spleen and the kidneys were not palpable, and no masses or tenderness could be detected.

The genitalia were those of a normal male infant.

No gross abnormalities were noted in the extremities.

The reflexes were physiologic.

Psychiatric Examination.—The infant did not talk and made no effort to do so. He seemed aware of his environment and tried to reach for objects. He could sit unsupported but did not walk. He fed himself with a spoon. His expression

was dull, usually staring. He did not become elated over anything, but was extremely irritable when his favorite toy was taken from him. His bowel habits were regulated.

Laboratory Examinations.—Urinalysis gave essentially negative results. The hemoglobin content of the blood was 80 per cent (Sahli), or 11.8 Gm. per hundred cubic centimeters. The red blood cells numbered 4,200,000 and the white cells 8,500, with polymorphonuclear leukocytes 22 per cent, lymphocytes 84 per cent, monocytes 2 per cent and eosinophils 2 per cent. The fasting blood sugar content was 89 mg. per hundred cubic centimeters. In the dextrose tolerance test (done under fasting conditions, with 1.5 Gm. of dextrose per kilogram of body

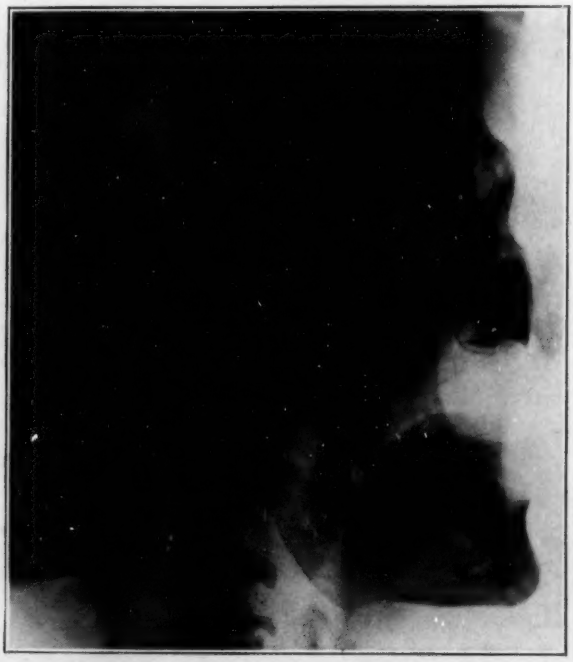

Fig. 2.—Roentgenogram of the jaw. Note the complete absence of teeth in the mandible. Only two unerupted teeth may be seen in the upper jaw.

weight) the following blood sugar values were obtained: one hour, 91 mg. per hundred cubic centimeters; two hours, 89 mg. A culture of the blood showed no growth in two weeks. The calcium content of the blood was 10 mg. per hundred cubic centimeters, the phosphorus content 5.6 mg., the chloride content (serum) 585 mg. (as sodium chloride) and the cholesterol content 114 mg. The Wassermann and Kahn reactions of the blood were negative. Gastric analysis (after fasting) revealed acid 100 and free acid 35. The sulfur content of the finger nails on Aug. 22, 1940 was 1.93 per cent; on September 29, 1.90 per cent, and on October 1, 2.76 per cent (average normal, 2.84 to 3.12 per cent).

Roentgenologic Examinations (Dr. Herman Ostrum).—Skull (fig. 2): The anterior and posterior fontanels were closed. The sella turcica was normal. There

were no teeth in the lower jaw, but there were two incisors in the upper jaw. Both mandibles were normal.

Chest: The pulmonary fields were clear. The cardiac silhouette was normal. The third, fourth and fifth ribs were joined in the right anterior axillary line.

Long Bones: There was no decalcification of the long bones. The centers of ossification were normal for a 17 month old infant.

Biopsy of Skin from Axilla (Dr. Fred Weidman).—"Two samples were submitted, one of which has been sectioned perpendicular to the skin (fig. 3). The tissue does not contain the subcutaneous fat, but, in any event, sweat glands were not discovered at any place in the section. It seems safe to conclude that there

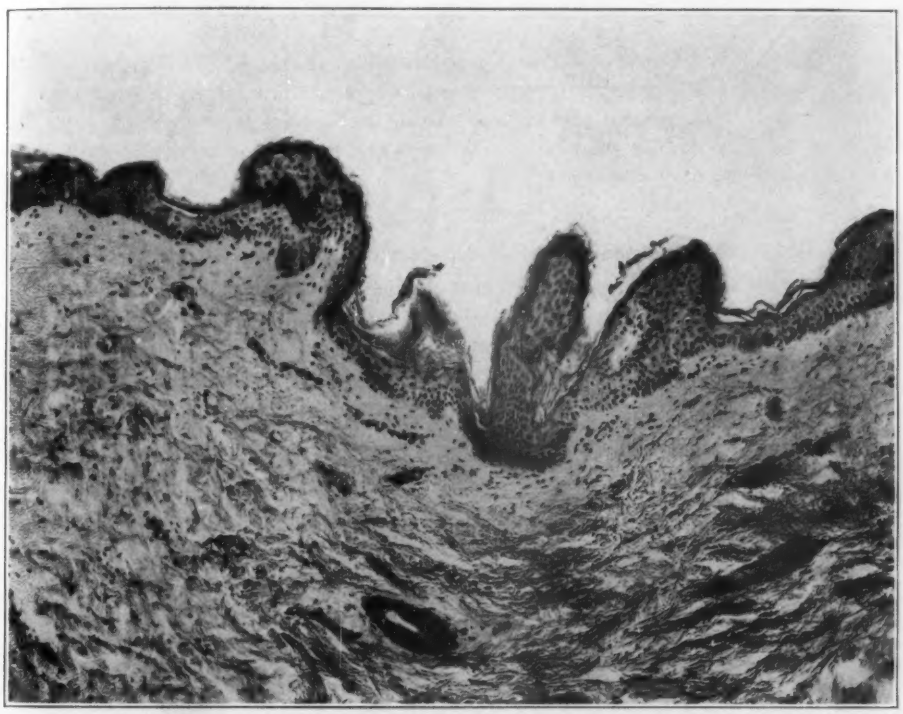

Fig. 3.—Section of skin from the axilla, showing absence of sweat ducts (× 250).

were not any sweat glands in this part of the body. The epidermis is probably normal; its thinness can be reasonably accounted for on the basis of the anatomic location and the age of the patient. There are fairly numerous hair follicles and associated sebaceous glands. Both of these structures are extremely small.

"The features are compatible with what should be expected in congenital ectodermal defect."

Course in the Hospital.—Two hours after admission the patient's rectal temperature rose to 108 F. Administration of sulfanilamide in full doses was started. Antipyretics and tepid sponging failed to bring the temperature down. The infant was given a gradually cooled bath, and the temperature fell to 101 F. in one hour.

Two hours later the temperature rose to 107 F., and another bath brought it down to 102 F. It remained at this level for twenty-four hours and then gradually returned to normal. There occurred a general cooling of the weather coincident with the drop in the patient's temperature. When the fever subsided, the rash previously noted gradually faded. During the period of hyperpyrexia the patient was given an injection of 1/96 grain (0.625 mg.) of pilocarpine hydrochloride. No sweating resulted. The infection of the upper respiratory tract rapidly disappeared, and the left ear cleared. During the infant's three and a half months' stay in the hospital he exhibited occasional bouts of fever for no apparent reason, but it never was extreme. He was definitely allergic to certains foods, for he would have acute attacks of urticaria after meals. Cutaneous tests were not done, but elimination of eggs from the diet apparently controlled the allergy.

Course After Discharge.—The patient has led an uneventful life since leaving the hospital. He has returned to the outpatient department, where it has been observed that his general physical and mental development is progressing satisfactorily. Up to the time of this report, only the two teeth noted on the roentgenogram have erupted.

COMMENT

We have presented a case of ectodermal dysplasia of the anhidrotic type with the following main features: (1) hypotrichosis (a fine fuzz on the scalp and no hair anywhere else on the body); (2) absence of sweat glands with intolerance for heat; (3) delayed dentition and roentgenologic evidence of almost complete edentia; (4) delayed mental and physical development; (5) allergic phenomena, as manifested by cutaneous sensitivity; (6) failure of lacrimation; (7) atrophic rhinitis; (8) a negative family history of the disease as far as could be determined; (9) a history of repeated infections of the upper respiratory tract of unusual severity; (10) a decreased sulfur content of the nails, and (11) a high sugar tolerance.

The allergic reactions noted in this patient have been reported by others.[2] It will be interesting to observe whether the child shows more severe forms as he grows older. The decreased sulfur content of the nails may have been merely a reflection of the patient's general malnutrition when he was first admitted to the hospital, as normal values were obtained after the diet had been enriched with sulfur-containing foods. This patient presented no clinical or laboratory evidence of endocrine dysfunction. Normal centers of ossification indicated normal thyroid function.

As the child grows older it will be necessary to have suitable artificial dentures made at frequent intervals and he will need careful guidance in adjusting his life to his condition. He probably will be safer in and better suited for the comparatively plain existence of farm life in a temperate, moist climate.

SUMMARY

Ectodermal dysplasia of the anhidrotic type is discussed from the standpoint of symptomatology and etiology. In view of the increasing evidence of the hereditary nature of the condition, the term "congenital" should be discarded. A case of the fully developed form with all the classic symptoms is presented.

Mr. T. V. Letonoff, division of biochemistry of the laboratories of the Philadelphia General Hospital, made the sulfur determinations.

Progress in Pediatrics

NUTRITIONAL REQUIREMENTS OF CHILDREN

A RÉSUMÉ

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The daily allowances shown in the accompanying table are recommended by the Committee on Food and Nutrition of the National Research Council (May 1941) and the Committee on Vitamins of the American Academy of Pediatrics. They are ample for healthy children of average size and activity with normal alimentary absorption. They need be increased only if the child is exceptionally large or active or has fever (more calories, thiamine and ascorbic acid are necessary). Care should be taken that the vitamins of the food are not destroyed by excessive cooking; thiamine and ascorbic acid may thus be lost.

The allowances in the table for vitamin A are suitable if the diet provides this substance partly in the colorless form and partly as the pigment carotene (provitamin A) of green and yellow vegetables. If the diet provides chiefly carotene the allowance should be increased because of less complete absorption.

For the vitamin content of foods consult the tables of any suitable recent textbook, such as that of Sherman and Lanford [1] or that of Hawley and Maurer-Mast.[2]

Except for vitamin D, these allowances can be met by a good diet of natural foods, which also will provide the other vitamins and minerals not listed in the table (vitamins B_6, E and K). All infants, whether breast or artificially fed, under 2 years of age should be given daily: 30 mg. (½ grain) of ascorbic acid (dissolved in a teaspoon of water and then added to the milk) or 4 tablespoons of tomato or orange juice to prevent scurvy, 5 drops of percomorph liver oil (added to the milk) or 2 teaspoons (10 cc.) of cod liver oil to prevent rickets and

From the Departments of Physiology, Nutrition and Pediatrics, Duke University School of Medicine.

1. Sherman, H. C., and Lanford, C. S.: Essentials of Nutrition, New York, The Macmillan Company, 1940.

2. Hawley, E. E., and Maurer-Mast, E. E.: Fundamentals of Nutrition, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

tetany and approximately 1 Gm. (15 grains) of calcium in the form of 1½ pints (750 cc.) of breast, whole lactic acid or sweet milk or as calcium chloride, lactate or gluconate. The amounts of calcium and protein needed are less if furnished by breast milk. The vitamin D may also be supplied as viosterol in oil, halibut liver oil (capsules for older children), cod liver oil reenforced with viosterol or crystalline vitamin D_2 in propylene glycol. Children soon become accustomed to the taste of cod liver oil, especially if it is kept and served ice cold. For older children it should be "floated" on ice cold tomato juice. The main objection to cod liver oil is the parental dislike of its odor. The nurse or

Daily Allowances of the Various Dietary Essentials for Children

Age, Years	Calories	Protein, Gm.	Calcium, Gm.	Iron, Mg.	Vitamins					
					A,* U. S. P. Units	Thiamine Hydrochloride,† Mg.	Riboflavin, Mg.	Nicotinic Acid, Mg.	Ascorbic Acid,‡ Mg.	D,§ U. S. P. Units
Under 1.....	100 per kilogram	3-4 per kilogram	1.0	6	1,500	0.4	0.6	4	30	400-800
1 to 3.....	1,200	40	1.0	7	2,000	0.6	0.9	6	35	400-800
4 to 6.....	1,600	50	1.0	8	2,500	0.8	1.2	8	50	400-800
7 to 9.....	2,000	60	1.0	10	3,500	1.0	1.5	10	60	400-800
10 to 12.....	2,500	70	1.2	12	4,500	1.2	1.8	12	75	400-800
13 to 15 (girls)..	2,800	80	1.3	15	5,000	1.4	2.0	14	80	400-800
13 to 15 (boys).	3,200	85	1.4	15	5,000	1.6	2.4	16	90	400-800

* One drop of percomorph or halibut liver oil contains 1,200 U. S. P. units of vitamin A; 1 teaspoon (5 cc.) of cod liver oil contains 400 U. S. P. units.

† Three milligrams of thiamine hydrochloride equals 1,000 U. S. P. units of vitamin B_1.

‡ One milligram of ascorbic acid equals 20 U. S. P. units of vitamin C. Fresh citrus fruit juices contain an average of 0.5 mg. per cubic centimeter (15 mg. per ounce). Canned citrus or fresh tomato juice contains one half and canned tomato juice one quarter as much.

§ Two drops of percomorph liver oil, cystalline vitamin D_3 (calciferol) in propylene glycol or viosterol in oil or 1 teaspoon (5 cc.) of cod liver oil contains approximately 400 U. S. P. units of vitamin D.

mother should always give cod liver oil with a smile to produce a favorable impression on the child; giving it all in one dose (not in milk) at the time of the bath is the least "messy" method. If an infant persistently dislikes cod liver oil and "sputters" while taking it, lipid pneumonia may ensue; such an infant, and also a premature or weak infant, should be given a small amount of a concentrated preparation.[3] The vitamin A

3. Five drops of percomorph liver oil may be given. Vitamin A and D concentrates in oil may also be used, e. g. 5 drops of afaxin in oil (Winthrop Chemical Company; 1,600 U. S. P. units of vitamin A per drop) and 5 drops of drisdol (vitamin D_3) in propylene glycol (Winthrop Chemical Company; 250 U. S. P. units of vitamin D per drop). There are available through health departments gelatin bottle neck capsules containing 3,000 U. S. P. units of vitamin A and 800 U. S. P. units of vitamin D per capsule. The tubular protrusion of the bottle neck may be snipped off and the contents squeezed directly on the infant's tongue or into his formula or orange juice.

but not the vitamin D content of cod liver oil deteriorates if the oil is not kept cold. Rancid cod liver oil may cause digestive disturbances. Part of the vitamin D may also be supplied in the form of irradiated or vitamin D milk.

The vitamin, calcium, iron and food allowances should be increased for premature infants. Ascorbic acid and percomorph liver oil are the cheapest sources of vitamin C and of A and D, respectively. For children over 2 years of age, the following daily diet will supply all of the various dietary essentials: a pint (500 cc.) of milk, one serving of lean meat (cheap cuts are just as nutritious), one egg (or equivalent protein, e. g. navy beans), one green or yellow vegetable, one citrus fruit (or tomato), two slices of whole grain or enriched bread, one square of butter (or oleomargarine with added vitamin A) and other foods to satisfy the appetite. Older children and adults also need vitamin D, and if it is not available from sunshine they should take the aforementioned doses of cod liver oil.

The six major deficiency conditions of children are rickets, tetany, scurvy, pellagra, beriberi and vitamin A deficiency. The daily amounts of the vitamins needed for the treatment of these deficiencies are approximately ten times the allowances shown in the table.

Water and fluid are necessary for the metabolism of food and excretion of its end products, for conservation and distribution of food in solution or in suspension throughout the body, for regulation of body temperature, for maintenance of the blood volume, for lubrication and protection of joints and organs (such as the heart) and for maintenance of the volume of the secretions, which contain 8 to 40 per cent water. The daily amount of fluid, including that in the diet, needed up to the age of 2 is 150 cc. per kilogram of body weight (2 ounces per pound); for children from 2 to 6 years old 100 cc. per kilogram (1½ ounces per pound) is necessary and thereafter 60 cc. per kilogram (1 ounce per pound). Older children should take at least 1,000 cc. (over a quart) of fluid daily. These amounts should be increased, parenterally if necessary, during hot weather or periods of vomiting or diarrhea. Five-tenths gram (7½ grains) of salt tablets or bouillon cubes, which contain 2.4 Gm. (37 grains) of salt, dissolved in a cupful of hot water and then cooled should be given frequently during the summer. When too much water is retained by the body, i. e. in the form of edema, it can be eliminated by salt-free diets, reduction of the fluid intake, sweating, catharsis, diuresis and raising the protein content of the serum. Prolonged fluid therapy depletes the thiamine content and requires administration of this substance; tetany also may be produced. Too little body fluid (dehydration or anhydremia) can be corrected by parenteral injections. The most obvious test of adequate water supply

to the body is that the urine output and dilution increase markedly after drinking a large quantity. The Aldrich-McClure cutaneous test also may be used to determine the degree of hydration.

The caloric requirements of children depend on such factors as the following: basal metabolism, muscular activity (crying can increase the total metabolic rate 100 per cent, and light work raises the caloric output 75 calories per hour), rate of growth, type of diet (specific dynamic action of food), fatigue, training, sleep, mental state, external temperature (less food in hot weather), heredity and utilization (some children gain on less food than others). The usual minimal and maximal requirements for an infant less than 1 year of age are 90 and 150 calories per kilogram (40 to 70 calories per pound); some infants gain satisfactorily on less; in fact, reducing the caloric intake of some infants who are not thriving may cause them to gain. Premature and undernourished infants may require 120 to 150 calories per kilogram (55 to 70 calories per pound). After the age of 1 year is reached a diet containing 90 calories per kilogram usually is adequate for a normal child. The amount of food required for an infant who must be fed artificially can be calculated as follows: The infant's weight in kilograms multiplied by 100 (calories per kilogram), or in pounds multiplied by 45, indicates the necessary caloric content of the diet for twenty-four hours.

The caloric content of the usual diets is: protein, 10 to 15 per cent; carbohydrates, 65 to 80 per cent, and fats (including unsaturated fatty acids), 10 to 20 per cent. Approximately 3 Gm. of protein per kilogram (1/20 ounce per pound) of body weight is essential. The minimal amount of carbohydrate necessary to maintain water balance and to prevent ketosis and depletion of the glycogen reserve of the liver is approximately 3 Gm. per kilogram of body weight per day for infants and slightly less for older children, i. e. 10 to 15 per cent of the total energy requirement. The optimal amount is approximately four times this minimum. These requirements are met for infants by a diet derived two-thirds from milk and one-third from added carbohydrate. A certain minimum of fat is indispensable. Diets which contain more than 6 Gm. of fat per kilogram (1/10 ounce per pound) of body weight, i. e. 15 to 30 per cent of the total calories, interfere with digestion and absorption and delay the emptying time of the stomach. Certain unsaturated fatty acids, e. g. linoleic acid, are necessary for normal nutrition. Carbohydrates also are essential for the complete oxidation of fat. Ten of the amino acids occurring in proteins are indispensable. Milk, eggs and meat are excellent protein sources of these amino acids. Individual cereals or legumes may lack one or more of the amino acids, although there are some exceptions, such as the soybean. Mixtures of several cereals and legumes are good sources.

In addition to calcium and iron, given in the table, the following minerals are essential: phosphorus, copper, iodine, sodium chloride, magnesium, potassium, manganese, cobalt, fluorine, nickel, silicon, sulfur and zinc. It may be assumed that all of these minerals will occur in sufficient quantities in a diet of natural foods with the possible exception of iodine and of sodium chloride. In regions of alkaline soil deficient in iodine, it is necessary to insure ingestion of sufficient iodine by the use of iodized salt. There may also be need in hot climates to add sodium chloride to the food in order to make up for the large loss incurred in sweating.

SYPHILITIC AORTITIS OF CONGENITAL ORIGIN IN YOUNG CHILDREN

REVIEW OF THE LITERATURE AND REPORT OF A CASE

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Spirochaeta pallida is known to affect every organ in the human body. It has been found in practically every organ in stillborn syphilitic infants and in newborn infants that have died of syphilis. The presence of S. pallida in the newborn on necropsy has been amply demonstrated by McCord [1] and others. Apparently these lesions heal rapidly if antisyphilitic treatment is instituted early in life. It is for this reason that one does not see later in life some of the stigmas of syphilitic infection observed in young children. This is especially true of the heart and the circulatory system.

While the occurrence of syphilitic aortitis in young children is of great interest to the clinician, no one has yet reported an authentic case of syphilis of the large vessels in early life diagnosed on clinical examination. Only on necropsy has it been possible to prove definitely that syphilis attacks the aorta and the adjacent large vessels in young children with congenital syphilis.

Norris [2] reported 2 interesting cases of syphilitic aortitis with confirmatory observations at necropsy. His first case was that of a child 9 years of age who had been well until four days before admission to the hospital. He came in a semiconscious condition. Roentgen ray examination of the chest showed an enlarged heart and a possible consolidation of the lower lobe in the right lung. The patient died the next day.

The necropsy revealed the following picture: The lesions were primarily in the aortic valves, which were thickened at the base; there was also a marked separation of the cusps. The sinuses of Valsalva

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1. McCord, J. R.: Two Hundred and Forty-Three Fetal Autopsies: A Syphilitic Study, J. A. M. A. **88**:620-628 (Feb. 26) 1927.

2. Norris, R. F.: Syphilitic Aortitis in Childhood and Youth: Report of Two Cases with Sudden Death, Bull. Johns Hopkins Hosp. **57**:206-217 (Oct.) 1935.

and the ascending aorta showed a thickened wrinkled intima with dilatation of the lumen. The process stopped abruptly at the beginning of the transverse arch. The coronary arteries were narrowed but not occluded. When the sections of various organs were stained, S. pallida was not found.

The second case was that of a youth 17 years of age. He came to the hospital in collapse and died shortly after admission. He had never been ill previous to that time. In this case also the autopsy revealed syphilis of the aorta, the sinuses of Valsalva, and the aortic valve. In addition, there was a stenosis of the left coronary orifice and occlusion of the right.

This author concluded that, although a Wassermann test was not obtained in these cases, the appearance of the aorta showed evidence of syphilitic aortitis. He pointed out the possibility that the patients had acquired the disease extragenitally. In order to prove syphilitic aortitis to be of congenital origin, he said, it would be necessary to show (1) that the mother unquestionably had syphilis at the time of the child's birth and (2) that the patient had other lesions of congenital syphilis or was known to have had a positive Wassermann reaction at an early age.

The 2 cases that Norris presented were noted among 14,000 consecutive autopsies at the Johns Hopkins Hospital—an incidence of only 0.014 per cent.

The occurrence of sudden death in these 2 cases is of special interest. It is especially to be noted that there was a distinct encroachment of the syphilitic process on the orifices of both coronary arteries in the first case and that the right coronary artery was completely occluded and the left distinctly narrowed in the second case. Norris agreed with other investigators that syphilitic aortitis may cause coronary occlusion, and that persons with this disease may die a coronary death.

Stolkind,[3] in reviewing the literature of hereditary syphilitic aortitis, reaffirmed the fact that S. pallida has been found in the blood vessels and heart in cases of congenital syphilis in stillborn infants and premature infants who died soon after birth. He reviewed the literature and gave numerous citations of European authors who have described the finding of S. pallida in babies as stated above. He emphasized this point, however, which is indeed important: that there is an absence of S. pallida in the wall of the aorta of children with congenital syphilis who are over 1 year of age.

Numerous writers have found certain definite changes of the large blood vessels in fetuses and in stillborn infants, consisting of cellular

3. Stolkind, E. J.: Hereditary Syphilitic Aortitis, Brit. J. Child. Dis. **17**:126-132 (July-Sept.) 1920.

infiltrations in the media and to some extent in the adventitia and also of hyperemia of the vasa vasorum. In children who have lived as long as three weeks there were found a partial or complete obliteration of the vasa vasorum in the media and adventitia and a growth of interstitial tissue.

According to Stolkind, the writers who described these changes expressed the belief that they are produced by syphilitic infection, which in general causes early death. Some authors who have examined many syphilitic fetuses have not found similar pathologic changes and have concluded that these vascular lesions may not be specific of hereditary syphilis. It is known, however, that lesions of syphilitic aortitis in adolescents are definitely characteristic.

After a study of these cases and of the opinions of other authors, Stolkind still expressed doubt as to the possibility of the presence of syphilitic aortitis in older children. He especially mentioned the case of a girl 14 years of age who on examination was found to have Hutchinson teeth, syphilitic ulcers on the left leg and on the abdomen, an enlarged liver, aortic regurgitation and ascites. The Wassermann reaction was repeatedly positive. There was also a history of chorea. On autopsy no syphilitic disease of the circulatory system was found, nor were there any signs of hereditary syphilis in the viscera.

An interesting case of productive aortitis with multiple aneurysms in a child, a white girl 10 years of age, was reported by Neiman and Marks.[4]

The family history revealed little of importance, and the Wassermann and Kahn tests of the father and mother were negative. On admission the child showed nothing of importance pertaining to the circulatory system. There was diminished resonance in the base and in the upper third of the right lung posteriorly. The heart was within normal limits, and no murmurs were elicited.

At that time a diagnosis of pulmonary tuberculosis with papulonecrotic tuberculids was made. The Mantoux reaction was positive with a dilution of 1:10,000. Later the patient became weaker and had attacks of dyspnea and slight elevation of temperature. There was some edema in the face. The radial pulse of the right arm was palpable and strong, but the radial, brachial and axillary pulses of the left arm were absent. There was a marked heaving precordial pulsation, and the cardiac dulness was transversely widened. On reexamination of the chest by roentgenograms, there seemed to be a mass in the mediastinum.

The autopsy revealed a primary tuberculous lesion in the apex of the upper lobe of the left lung and many features of ascites. Endocarditis

4. Neiman, B. H., and Marks, M. B.: Productive Aortitis with Multiple Aneurysms in a Child, Am. J. Dis. Child. **59**:571-578 (March) 1940.

minima was present on the aortic valve, and the heart showed left ventricular hypertrophy and sclerosing aortitis of the ascending and thoracic portions, with formation of four aneurysms and compression of the left subclavian artery by one of these aneurysms.

At the valve the aorta measured 50 mm. in circumference. The leaflets were thin, and on the free margin of the posterior leaflet were single pinpoint-sized translucent nodules. The wall of the aorta was thickened in places up to 5 mm. In numerous areas the intima was wrinkled and puckered. Posterior and lateral to the origin of the left subclavian artery and slightly compressing it, there was an outpouching of the wall 2 cm. in diameter. The intimal lining of the pouch was extremely wrinkled, and in the lumen there was an adherent purple-gray blood clot. The sinus of Valsalva of the right aortic leaflet revealed an aneurysmal outpouching 12 mm. in diameter. Above the middle leaflet there was an 8 mm. outpouching, and a fourth outpouching, 9 mm. in diameter, was present 4 cm. above the valve. The thoracic aorta showed similar wrinkling and puckering, and in the lowermost portion there were two areas, 2 cm. long, in which the intima was covered by adherent blood clots. In these areas the intima was roughened. The circumference of the thoracic aorta was 62 mm.; that of the abdominal aorta was 30 mm. At and below the level of the diaphragm the intima was smooth.

The outstanding point in the microscopic examination was that the aorta had all the characteristics of syphilitic aortitis as observed in the acquired form of the disease.

Neiman [5] has described certain pathologic lesions of the large artery in rheumatic fever. Pappenheimer and Von Glahn [6] have described a distinctive lesion of the aorta in rheumatic fever. This lesion is found in the form of a scar, roughly the shape of an inverted wedge. It is often acellular and is located in the region of the nutrient vessels of the media.

Neiman and Marks stated their belief that although aneurysms are seen in rheumatic aortitis, they are less common than in syphilitic aortitis. They felt certain, moreover, that there had been no history of rheumatic fever in this patient. They stated, therefore, that they had presented a case of productive aortitis with four thoracic aneurysms in a child 11 years of age, and they suggested that syphilis might be the cause; but they had no way of establishing the fact that this condition might be due to congenital syphilis.

5. Neiman, B. H.: Verrucous Aortitis with Special Regard to Aneurysm Formation in Children, J. Lab. & Clin. Med. **19**:929-942 (June) 1934.

6. Pappenheimer, A. M., and Von Glahn, W. C.: Lesions of Aorta Associated with Acute Rheumatic Fever, and with Chronic Cardiac Disease of Rheumatic Origin, J. M. Research **44**:489-505 (Sept.) 1924.

In 1932 McDonald [7] reported a case of syphilitic aortitis in a patient 9 years of age. Two years later he was able to make a study of 11 cases of syphilitic aortitis, in most of which the patients were admitted to the Royal Victoria Infirmary, Newcastle-on-Tyne. He stipulated the following criteria for distinguishing between the congenital and the acquired type: (1) a significant clinical history, with special reference to family history; (2) physical signs of latent syphilis; (3) a symptom complex suggestive of aortic disease, especially if associated with an accentuated aortic second sound; (4) a positive Wassermann reaction; (5) positive orthodiagraphic findings; (6) certain abnormal electrocardiographic findings; (7) alleviation of aortic symptoms after specific treatment.

McDonald expressed the belief that the main aids in separating the two types are the clinical history with special reference to family history,

Cases of Syphilitic Aortitis as Reported by McDonald and Others

Group 1 Previously Reported Congenital			Group 2 Present Series Congenital			Group 3 Present Series ? Congenital		
	Sex	Age	Case No.	Sex	Age	Case No.	Sex	Age
Nixon	F	20	1	M	22	4	M	24
Turnbull	F	17	2	M	21	6	F	26
Turnbull	M	7	3	F	19	8	M	30
Von Zetkowsky	F	17	5	F	19	9	M	29
Paul	F	18				10	F	30
Schulte	M	13						
Martland	M	10						
McDonald	M	9						
Average = 14 yr.			Average = 20 yr.			Average = 28 yr.		

and also, if possible, physical evidence of latent syphilis which may justify one in making a diagnosis of congenital syphilis. He also mentioned the fact that Coombs believed the latent period between primary infection and the onset of cardiac symptoms to be between fifteen and twenty-five years, and that it would therefore seem likely that syphilitic aortitis encountered in the first two and one-half decades would more probably be of congenital origin.

It is known, however, that a virulent syphilitic infection may be so overwhelming in character as to cause this condition to occur earlier, and the possibility of primary extragenital infection in infancy must not be overlooked.

McDonald repeated what other writers have reported, that there is a definite tendency to spontaneous recovery in congenital syphilitic aortitis, and that in this respect there may be a similarity between con-

7. McDonald, S., Jr.: Syphilitic Aortitis in Young Adults with Special Reference to a Congenital Aetiology, Brit. J. Ven. Dis. **10**:183 (July) 1934.

genital syphilis and tuberculosis. For instance, in pulmonary tuberculosis of infants there is a noticeable tendency to spontaneous recovery, but in some cases, in which the resistance is low, the disease may run a fulminant course. Thus in most cases the patient seems to have acquired an immunity to adult tuberculous infection of the respiratory tract, while in the rest, who become allergic, pulmonary reinfection shows no spontaneous tendency to resolve, and unless there is adequate treatment the disease progresses actively. For that reason, McDonald suggests that the possibility of syphilitic allergy may have a bearing on the problem of aortitis in patients with hereditary syphilis.

In conclusion, he stressed the importance of excluding syphilitic aortitis before making a clinical diagnosis of rheumatic heart disease in young adults. After following the outline of the seven specific criteria as a basis for diagnosis of congenital syphilitic aortitis, he felt that in a large proportion of the cases in his report the disease was of congenital origin or was possibly due to superinfection or reinfection of allergic persons with hereditary syphilis.

We wish to report the following case.

REPORT OF CASE

A. K. V., a Negro girl 9 years of age, was admitted to the Grady Hospital April 19, 1941. Her chief complaints were shortness of breath, vomiting and pain in the stomach and chest. Her mother said that the onset of this illness was rather sudden. About three weeks before we saw her, for no apparent reason, she vomited her breakfast. She continued to be nauseated and vomited five or six times a day for about four days. On two occasions the vomitus contained a little red clotted blood. Up to her admission to the hospital the child did not remain entirely at rest, but stayed in the house. On slight exertion she had to discontinue her play on account of shortness of breath. During those three weeks she suffered from orthopnea during the night.

About ten days before the patient came to the hospital a cough developed; it was productive, and the mucus was tenacious. Two days before entering the hospital she noticed a growing pain around the umbilicus. (The pain was intermittent, and she continued to complain of this symptom after her admission.) Late in the afternoon of the same day she complained of a pain in the left side of the chest. Her mother said that she had had no elevation of temperature before that day, but she also estimated that the child had lost about 6 pounds (2.7 Kg.) since the onset of the illness.

The parental history is irrelevant except for the fact that when this child was born the mother's Wassermann reaction was positive. At that time a strongly positive Wassermann reaction was obtained with the child's cord and sinus blood. The mother received no treatments at any time, and neither did the child. The mother had had no miscarriages, and she had borne two more children, who were alive and well.

There was no history of tuberculosis in the family. At birth the patient had no eruption of any kind and seemed to be physically normal in every way. Her development was normal. She had suffered from no childhood diseases except

whooping cough, which she had at the age of 7, with no complications resulting. She had occasionally suffered from frontal headaches and once or twice a year had had colds and what she termed as sore throat of no severe nature. She had not suffered from shortness of breath or pains in her joints and, in fact, had been what one might term a well child.

Physical Examination.—On admission the patient had a temperature of 101 F., a pulse rate of 136, a respiratory rate of 26 and a blood pressure of 116 systolic and 70 diastolic. Her general appearance was that of an acutely ill child, she was obviously dyspneic and showed no abnormal movements of the body. Her skin was moist and hot, but there were no eruptions, pigmentations or petechiae. There was no edema, hemorrhage or sign of icterus. Her head was normal in shape and symmetric and there were no areas of tenderness or craniotabes.

The patient's pupils were round and equal and reacted to light. The conjunctivas had good color, and no petechiae were present. There was no discharge of any kind, no nystagmus and no paralysis of intraocular muscles. The mucous membranes of her nose were slightly injected. Her turbinates were slightly enlarged, and there was a mucoid discharge from her nose. There was nothing abnormal about the ears. It was difficult to see any cyanosis about the lips. Examination of the mouth showed the membrane to be of good color. The teeth were carious, but there were no Hutchinson teeth. The tongue had several transverse deep fissures. The tonsils were slightly hypertrophied and injected. The pharynx was slightly injected, and there appeared to be present a mucoid exudate. The neck was not retracted, and there was no rigidity. The vertebrae were normal.

On examination of the chest one could see the prominence of intercostal spaces. The respiratory rate was 36, and the patient was obviously dyspenic; Harrison's groove was not present. On examination of the lungs one could note increased tactile fremitus high in the right axilla and extending from the second to the fifth thoracic vertebra. The percussion note was somewhat impaired over both pulmonary fields, but it was high in the right axilla. Coarse and moderate moist rales were heard throughout both pulmonary fields. These rales were more prominent in the bases. Whispered and spoken voice sounds were transmitted more clearly in the right axilla than anywhere else.

On examination of the heart the cardiac impulse was found to be diffuse and very forceful; it was present in the fourth, fifth and sixth left intercostal spaces. The rate was 136 per minute, and the presence of a gallop rhythm was noted. A soft grade I systolic murmur was heard at the apex. On account of the increased rales over the whole lung and the rapidity of the heart beat, it was difficult to find whether these murmurs were transmitted or not. The cardiac dulness was definitely increased to the left and downward. On examination of the abdomen no muscular rigidity and no areas of tenderness were felt. There seemed to be no sign of fluid; the hepatic dulness extended to about 3 or 4 cm. below the right costal border. The kidneys and spleen were not palpable. The genitalia were normal; no scars or lesions were found, and there was no discharge. Nothing abnormal was found about the rectum; there were no condylomas. The nervous system revealed nothing abnormal. The only laboratory work done on the day of admission was a leukocyte count, which showed 16,400 cells, with nothing abnormal in the differential count, and a urinalysis, which showed 8 to 12 pus cells on the high power field.

The impression on admission was that the patient was probably suffering from (1) congestive heart failure, (2) rheumatic myocarditis with mitral valvulitis, (3) possible congenital syphilis and (4) chronic tonsillitis. There was also considered a possibility of pulmonary tuberculosis, bronchopneumonia and pericarditis.

Roentgen Examination.—On admission, fluoroscopic studies of the chest and heart revealed that there was a generalized enlargement of the heart in all diameters. The left atrium was slightly enlarged, sufficiently to compress the esophagus but not to deflect it. The left ventricle showed the most enlargement. The rate was slightly increased, the rhythm regular and the amplitude normal. There was no evidence of pericardial effusion. Passive congestion was slight.

Roentgenographic examination of the chest revealed enlargement of the cardiac shadow and a density radiating from both hili. The interlobar pleura of the right lung was thickened. Fluoroscopy was advised for the purpose of distinguishing

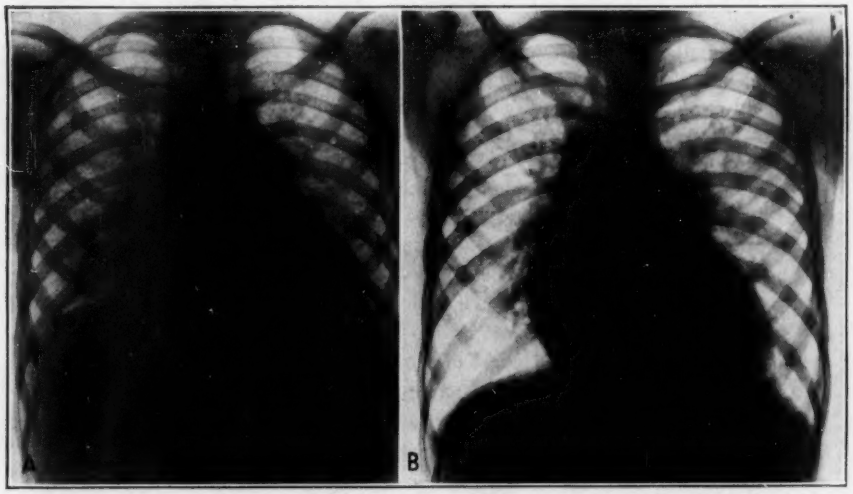

Fig. 1.—*A,* roentgenogram made on admission, showing enlargement of the cardiac shadow, the density radiating from both hili and thickening of the interlobular pleura of the right lung. *B,* roentgenogram made thirteen days later, revealing enlargement of the cardiac shadow as before and a definite density throughout the hilar regions and intermediate zone.

between pericardial effusion and cardiac enlargement, in order to determine whether passive congestion or bronchopneumonia was present.

Thirteen days later another roentgenogram of the chest was made. At this time there was a marked enlargement of the cardiac shadow, as described previously. There was a definite density through the hilar regions and the intermediate zone. The roentgenologist again advised fluoroscopy to distinguish between passive congestion and bronchopneumonia. His impression was that the patient suffered from the former. However, it was difficult to get permission for further roentgen examinations.

Laboratory Reports.—The patient's Kahn reaction was 4 plus. Her history revealed that at birth the Wassermann reaction of her cord and sinus blood was strongly positive but that she had received no treatment. The sputum showed a short chain streptococcus and many diplococci, which were not identified.

The blood showed a count of 4,150,000 red cells and 16,450 white cells; the differential count was of little importance. There was no sickling. Chemical examination of the blood revealed 28.5 mg. of nonprotein nitrogen and 1.1 mg. of creatine per hundred cubic centimeters. The sedimentation rate was 128 mm. per hour. Tuberculin tests gave negative results with various strengths. The calcium gluconate circulation time was fifteen seconds and the ether circulation time three to four seconds.

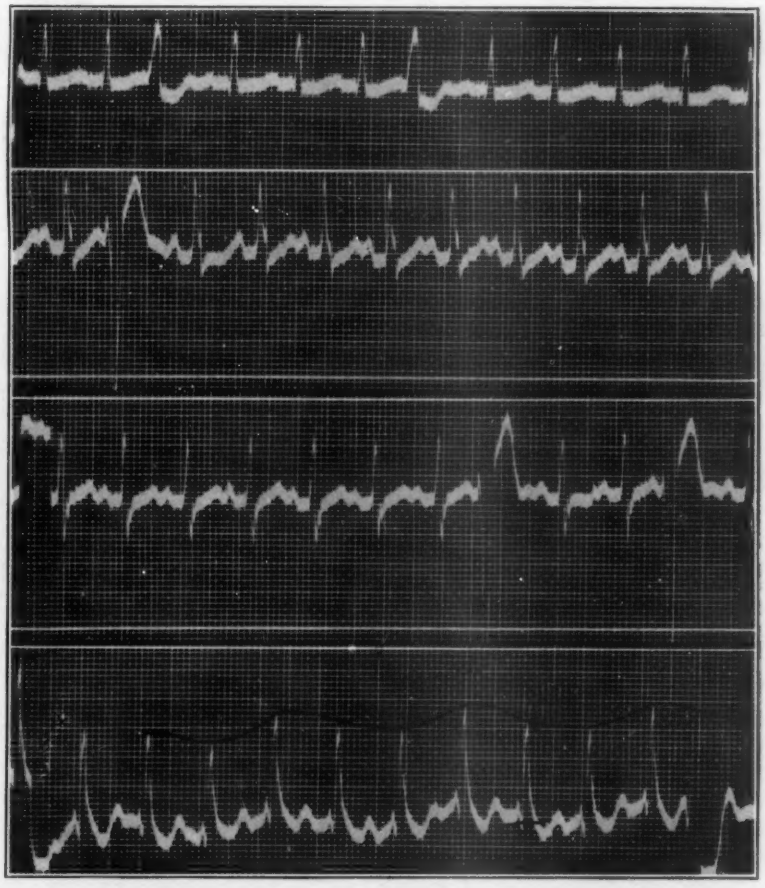

Fig. 2.—Electrocardiogram made April 25. Notice the slurring of the QRS complex throughout, the depression of the ST complex in leads I and II and the biphasic T wave in lead IV.

Progress Notes.—Three days after admission there was still a definite area of consolidation high in the right axilla with increased transmission of tactile fremitus. Two days later the patient was still orthopneic. Her pulse was slower, and her liver was only 1 cm. below the costal margin. The physical findings were now more indicative of passive congestion. The temperature remained between 99 and 100 F. by rectum; the respiratory rate was 32 and the pulse rate 136.

A systolic murmur was present. Salyrgan (5 cc. of solution) was given from time to time, but the patient's condition became much worse and she complained of abdominal pain. Three days before her death the rhythm was regular but the gallop was still present.

The patient gradually became worse and continued coughing up small clots of blood. She died three weeks after admission.

Electrocardiograms.—An electrocardiogram made on April 25 showed a rate of 138, a PR interval of 0.16 second, a QRS interval of 0.10 second, and a QT interval of 0.28 second. Ventricular passive congestion was found; the QRS complexes were slurred in all leads, and the ST complexes were slightly depressed in leads

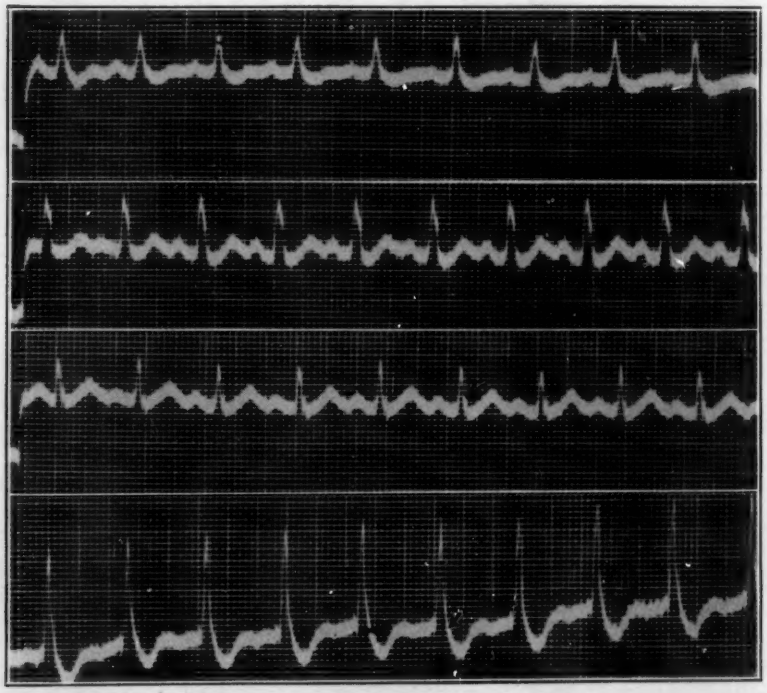

Fig. 3.—Electrocardiogram made May 4, showing slurred QRS complex in all leads, depression of the ST complex in leads I, II and IV and an inverted T wave in leads I and IV.

I and II. The T wave was biphasic in lead IV. The electrocardiogram gave the impression of (1) an intraventricular conduction defect; (2) myocardial disease (1 to 2 plus), and (3) ventricular passive congestion.

Another electrocardiogram was made on May 4. At this time the rate was 120, the PR interval 0.18 second, the QRS interval 0.10 second and the QT interval 0.36 second. The QRS complexes were slurred in all leads; the ST complexes were depressed in leads I, II and IV; the T wave was inverted in leads I and IV. These results led to the conclusion that there had been a definite change since the previous record, which suggested a changing myocardial process due to inflammation or coronary disease.

Report of Macroscopic Examination at Necropsy.—The body measured 46 inches (117 cm.) in length and was fairly well nourished. No body heat was present, and rigor mortis was noted throughout. The skin was darkly pigmented, dry and elastic. There were no skin eruptions, and no signs of an old exanthema were noted. The body showed average muscular and bony development. The hair on the head was black and was of negroid type.

The skull did not reveal any evidence of old or recent trauma. It appeared symmetric, and no exostoses were seen. The fontanels were closed. The eyelids appeared very slightly puffy, and the conjunctivas were pale and edematous. The pupils were round, dilated and of equal size. The corneas appeared clear. There was no injection of the corneas, and no cloudiness was evident.

There was no saddle nose. No fluid or blood escaped from the mouth, nose or ears. The teeth were in poor condition; however, none of the incisors were of the Hutchinson type. The tongue and the mucous membranes of the gums were covered by some whitish mucoid exudate. The tonsils appeared hypertrophic and injected. No scar tissue was noted in the gums or in the nasal septum. The lips were dry and were covered by brownish crusts. No fissures were seen. The trachea appeared in midline; the thyroid was not palpable.

The cervical lymph glands were not palpable. A moderate engorgement of the blood vessels of the neck was seen. The thorax appeared symmetric, and the intercostal spaces seemed shrunken. The breasts were not developed. The epigastric angle was acute. The liver was palpated in the right upper quadrant of the epigastrium. Its lower edge extended 8 cm. below the costal margin. No fluid wave was elicited. No hernias were evident and no operative scars were seen.

There was a very slight anasarca of the back. There was no pubic hair. The external genitalia appeared normal. The vagina did not reveal any evidence of a healed primary syphilitic lesion. The hymen was poorly developed, and the hymenal ring measured 1 cm. in diameter. The cervix and uterus appeared infantile on palpation. Rectal examination revealed nothing abnormal.

The extremities were symmetric. They did not reveal any deformities. There was no swelling of the joints. The epitrochlear lymph nodes were palpated on both sides. No clubbing of the fingers was noted. The nail beds had a cyanotic color.

Internal Description: The internal description was confined to the thoracic and abdominal cavities. The panniculus adiposus of the anterior abdominal wall was hardly developed. The muscles of the anterior abdominal wall appeared pale red, flabby, and somewhat wet. When the peritoneal cavity was opened, no free fluid was found. The liver extended 8 cm. below the costal margin, and its lower edge was markedly rounded. In the region of the spleen numerous dense fibrous adhesions were noted between the capsule and the parietal peritoneum. The loops of the small and large intestines were moderately distended. Otherwise the viscera occupied a normal position.

The sternum and the costal cartilages were normal. When the thoracic cavities were opened, about 50 cc. of clear amber-stained fluid was found in each pleural cavity. There were some fine adhesions between the posterior aspect of the upper lobe of the left lung and the parietal pleura. These adhesions were separated with ease. The parietal and visceral pleura otherwise appeared smooth and shiny. The right lung was purplish gray on the surface, and it felt firm on palpation. However, it was crepitant throughout, except in several small areas in the right lower

lobe which appeared firmly consolidated. Similar areas appeared in the left lower lobe. These areas presented on cut section a deep red color. Within the parenchyma of these areas several smaller grayish-yellowish areas were seen. The remainder of the parenchyma of the lungs had a reddish gray color, with a brownish tinge.

The parenchyma was very wet, and on compression of the lung tissue a large amount of frothy fluid escaped. The right lung revealed an anomaly, as it consisted of four lobes; the lower lobe seemed to be subdivided into two lobes. The right lung weighed 480 Gm., and the left lung weighed 410 Gm. The mucous membranes of the bronchi appeared congested and edematous. The tracheobronchial lymph nodes were somewhat swollen and anthracotic. The thymus gland was poorly defined. It consisted of several pinkish gray lobules and weighed approximately 15 Gm.

Fig. 4.—Thickening and rolling of the free margin of the pulmonary valve leaflets, with widening of the commissures.

On opening of the pericardial sac about 50 cc. of amber-stained fluid was found. This fluid contained some very delicate fibrin threads. A fine fibrin layer which appeared very edematous covered the proximal portion of the aorta. The heart appeared greatly enlarged, chiefly to the left and downward. On palpation it had a very flabby consistency. The left auricle was considerably distended. The myocardium had a pale red color and an opaque appearance. It measured 6 to 8 mm. in the left ventricle, and about 3 to 4 mm. in the right ventricle. There was a definite dilatation of the left ventricle. The trabeculae carneae and the papillary muscles were noticeably flattened. The endocardium was smooth and shiny. The leaflets of the tricuspid, mitral and pulmonary valves were smooth and pliable and did not reveal any pathologic changes. They measured 8.57 cm., 7 cm. and 4.8 cm. respectively. The intima of the aorta appeared edematous and was formed in

numerous longitudinal folds. The wall of the aorta measured about 4 mm. in thickness. A few yellowish patches appeared in the ascending aorta, but most of the intima had a whitish gray appearance. The commissures between the aortic cusps were widened, measuring 3 mm. The cusps were smooth and pliable. The ostia of the coronary arteries were much narrowed by the edematous intima of the aorta. The coronary arteries were left unopened at this time, in order to preserve the specimen for study after fixation. The foramen ovale and the ductus arteriosus appeared closed. The heart weighed 280 Gm.

The wrinkling and edema of the aorta were seen throughout the entire aortic arch. They were not noted in the thoracic aorta or the abdominal aorta, which contained a few yellowish flakes. The common carotid and subclavian arteries on the left side revealed an interesting anomaly, as they did not have an ostium in the aorta. They seemed to be of normal diameter, but their lumens started to be obliterated about 2 to 3 mm. from the wall of the aorta. They were felted with a whitish, partly organized blood clot. The intima of the distal portion of these vessels appeared perfectly normal.

The liver weighed 900 Gm. Its lower edge was distinctly rounded; the capsule was smooth and transparent and revealed a brownish red parenchyma, which was somewhat firm. Cut sections through the liver revealed a slight increase of the interstitial fibrous tissue. The central veins appeared very prominent, and the peripheral portion of the lobules had a somewhat yellowish brown color. The intrahepatic vessels and bile ducts were not dilated. The gallbladder was found in the usual position. It contained about 15 cc. of greenish bile. The mucosa was velvety, and no concretions were found in the gallbladder. The common, cystic and hepatic ducts were patent throughout.

The spleen weighed 110 Gm. Its capsule had a whitish gray appearance and was considerably thickened. The pulp had a firm consistency. There was a marked hyperplasia of the malpighian bodies. The parenchyma of the spleen had a dirty purplish gray color. The pulp was not wiped off with a knife. A moderate increase in the fibrous tissue was noted.

The adrenal glands appeared normal in size, shape and position. The cortex measured about 1 mm. in thickness and had a pale yellow color. The medulla had a pale grayish white color, and the parenchyma of the medulla appeared opaque throughout.

The kidneys were found in a poorly developed fat capsule. The capsule stripped with ease, revealing a lobulated, dark red, smooth surface. There was engorgement of the stellate veins. Cut sections revealed marked engorgement of all vessels. The architecture of the cortex and the medulla was well defined. The papillae had a deep red color. The renal pelves were not dilated, and the ureters followed the usual course. The bladder was empty.

The genital organs were infantile and did not reveal any gross pathologic changes.

The stomach contained some dirty greenish mucoid material. The mucosa was covered by a large amount of mucus and appeared swollen and edematous. It had a pinkish yellow color. The mucous membrane of the duodenum was stained with bile. No ulcerations were seen. Nothing remarkable was found in the remainder of the gastrointestinal tract. The intestinal lymph nodes were not enlarged.

The pancreas was of soft consistency and of prismatic shape; it had a grayish yellow, lobulated surface.

Anatomic Diagnosis: The macroscopic examination suggested diagnosis of the following: (1) syphilitic aortitis with aortic insufficiency and marked narrowing of the coronary ostia; (2) dilatation and hypertrophy of the left ventricle; (3) congestion and edema of the lungs; (4) bronchopneumonia (syphilis of the lungs, questionable); (5) hepatomegaly and splenomegaly; (6) perisplenitis; (7) congestion of all internal organs; (8) occlusion of the left common carotid and left subclavian arteries (congenital ?).

Résumé: This patient had severe syphilitic aortitis with aortic insufficiency, indicated by great widening of the commissures. The ostia of the coronary arteries appeared extremely narrow. Hypertrophy and dilatation of the left ventricle were noted. The aortitis seemed to be caused by congenital syphilis, though such a complication is rare. However, no primary lesion was found, and old hospital records indicated that the patient had had a positive Wassermann reaction at birth and after birth. She had apparently not been treated.

Report of Microscopic Examination at Necropsy.—Lungs: The capillaries in the alveolar walls were extremely congested with red blood cells. A large amount of edematous fluid was seen in the alveolar spaces. The alveolar spaces also contained a varying number of mononuclear cells which had about twice the diameter of red blood cells. These cells showed a fine pinkish-staining cytoplasm and a large round or oval nucleus. A small number of these cells was loaded with a fine granular brownish pigment. Red blood cells were also seen in the alveolar exudate, but practically no polymorphonuclear leukocytes were found. In one section a moderate increase of fibrous tissue was seen under the pleural surface. This fibrous tissue appeared very loose and edematous and contained occasionally a round cell infiltration. One section through the lungs showed an area of infarction. All of the alveoli in this section were filled with disintegrating red blood cells. The alveolar walls were still distinguishable. Some of the alveoli contained a fine meshwork of fibrin. A section through a small bronchus showed that the lumen of this bronchus was almost plugged up by a cellular exudate consisting mostly of polymorphonuclear cells.

Heart: The fibers of the heart muscle appeared hypertrophic and edematous but showed a fairly well preserved striation. Considerable fragmentation of the fibers had taken place. The interstitial tissue of the heart was very prominent and contained a large proportion of fat cells. In many small areas the fibers lost their striation, and their sarcoplasm assumed a pale-staining, granular appearance. The capillaries of the interstitial tissue appeared engorged. There were no interstitial inflammatory processes. The walls of the coronary arteries had the usual thickness and did not reveal any pathologic changes.

The auricular wall consisted of a large number of interlacing bundles of muscles and fibers, between which a loose edematous connective tissue appeared. There were no inflammatory changes. No Aschoff cells were evident.

Aorta: The innermost layer of the intima consisted of a hyaline tissue which stained deep red; it contained only a small number of nuclei. The outer layers of the intima were faintly stained, and showed numerous cholesterol clefts. There was no calcification. The media in some instances appeared slightly hyperplastic. The adventitia consisted of a thick layer of fibrous tissue which contained a large number of rather well defined round cell infiltrations. These round cell infiltrations were found mostly in the perivascular areas. Small groups of round

Fig. 5.—Cross section of the aorta, showing perivascular infiltration of adventitia.

Fig. 6.—Low power section of the aorta, showing perivascular infiltration of the vasa vasorum of the adventitia.

cells were seen around the small vessels penetrating into the media. Frequently the infiltrations were spread lineally between the adventitia and the media. In some areas of the media necrosis of the tissue seemed to have taken place. In these areas the elastic tissue was replaced by a rather dense fibrous tissue.

Right Internal Carotid Artery: There was much scarring of the aorta at the point where the right internal carotid artery emerged. There was also much lymphocytic infiltration at this point. The right internal carotid artery, as it emerged from the aorta, was almost entirely occluded by subintimal connective tissue proliferation. There was an attempt at recanalization by the development of multiple small vascular spaces lined by one layer of flattened endothelial-like cells. The adventitia here displayed focal areas and linear streaks of lymphocytic infiltration with increased fibrosis.

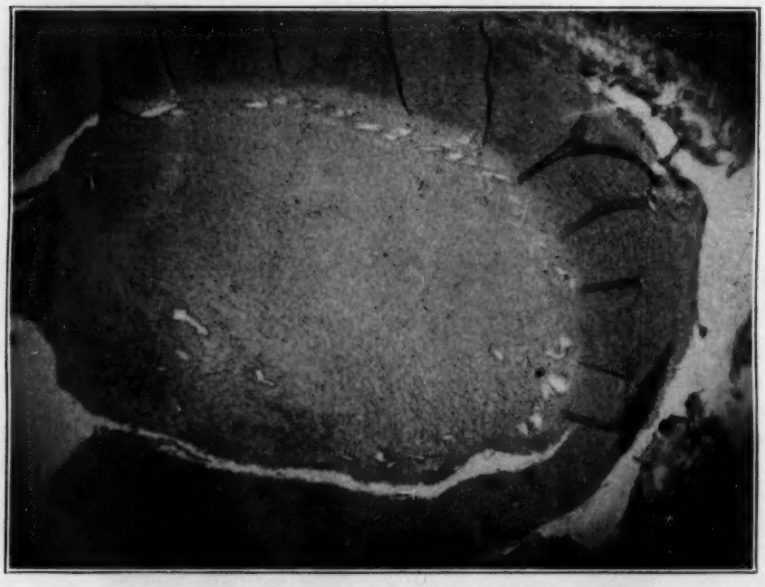

Fig. 7.—Internal proliferation and thrombosis, with beginning recanalization of the right internal carotid artery as it emerges through the wall from the aorta.

Liver: The triads of the liver revealed a slight increase of the connective tissue. The sinuses between the cell cords appeared distended and contained in some areas a large number of red blood cells. The epithelial cells had a granular cytoplasm and a round vesicular nucleus. The sections of the liver were otherwise not remarkable.

Spleen: There was decided hyperplasia of the lymph follicles. The germinative centers, however, were not clearly demonstrated. The sheathed arteries had a comparatively narrow lumen. The sinuses of the pulp were packed with red blood cells. The trabeculae appeared to be moderately thickened in diameter and showed beginning hyalinization.

Pancreas: A moderate increase of both interlobular and interacinar fibrous tissue was revealed. The epithelial cells showed rather marked albuminous degeneration. The islets were sharply defined and appeared apparently in a normal number. The small arteries did not show any pathologic changes. In some areas a necrosis of the epithelium was visible. There was, however, no inflammatory reaction.

Kidneys: Most of the glomeruli appeared active. The glomerular tufts did not show any inflammatory changes. There was no exudate in the capsule of Bowman. The epithelium of the tubules showed marked albuminous degeneration.

Fig. 8.—High power view of section of thrombosis through the right internal carotid artery.

The lumens of the convoluted and straight tubules were filled with a pinkish-staining granular material. The interstitial capillaries of the medulla were rather heavily congested. The walls of the arteries did not reveal any pathologic changes.

Adrenal Glands: The cortical layers were well defined. They consisted of cells with a foamy-appearing cytoplasm. The interstitial tissue of the medulla appeared somewhat edematous. The cytoplasm of the cells had a granular appearance. Most of the cells were basophilic. There were a few ganglion cells in the medulla.

COMMENT

We have presented the case of a Negro girl 9 years of age who came to the hospital complaining of shortness of breath, vomiting and pain in the stomach and chest. She was apparently well up to a few days before admission.

Her family history is of importance in this case only because the mother had a positive Wassermann reaction and the Wassermann reaction of the child's cord and sinus blood was also strongly positive. Neither the mother nor the child received any treatments.

On physical examination our attention was called especially to the heart. The rate was about 136 per minute, there was a gallop rhythm and a soft grade I systolic murmer was heard at the apex. The cardiac dulness was definitely increased to the left and downward.

On the basis of these features found on examination, it was proper to make a diagnosis of congestive heart failure following rheumatic myocarditis with mitral valvulitis. Even though the history revealed that a positive Wassermann reaction had been obtained both from the patient and from her mother, it could not at that time be assumed that this patient was suffering from an involvement of the circulatory system caused by congenital syphilis. The electrocardiogram suggested a myocardial infection, which was interpreted as being due to inflammation or to coronary disease.

After the necropsy it was possible to correlate the history with the postmortem observations. There was certainly no disease present from the pathologic standpoint in the tricuspid, mitral or pulmonary valves. The aorta, however, showed definite pathologic lesions, which could be attributed to a syphilitic infection. Along with these lesions, which have been previously described, we want to emphasize the involvement of the coronary arteries. The ostia of these arteries were markedly narrowed. Microscopically they were comparable to the description as given on macroscopic examination. Certainly, taking all these things into consideration, it is possible to make a diagnosis in this case of syphilitic aortitis with aortic insufficiency and narrowing of the coronary arteries.

Since there were no signs of lesions on the external genitalia that would lead us to consider the possibility of acquired syphilis, we must definitely exclude this as a factor in the cause of death. When a summary of the pathologic report is added to the previous findings, it is only logical to classify the condition as of congenital origin.

Death came in this case, as it may sometimes in cases of this nature, from an involvement of the coronary arteries.

SUMMARY

We have presented a patient 9 years of age with both a maternal and a birth history of syphilis.

Pathologically the aortitis has been diagnosed as of syphilitic origin, and we believe that the case must be classified as one of syphilitic aortitis due to congenital syphilis.

The difficulty in such cases is due to the fact that the diagnosis cannot be made clinically because rheumatic heart disease is sometimes suspected. Pathologically, however, rheumatic heart disease differs greatly from syphilitic aortitis, as may be seen in descriptions by McCord, Norris, Stolkind, Neiman and Marks, Neiman, Pappenheimer and Von Glahn, and McDonald.

Obituaries

ADALBERT CZERNY

1863–1941

On Oct. 4, 1941, at the age of 78, Prof. Adalbert Czerny died as the result of a cerebral accident. About a year previously he had had his first stroke, from which he had almost completely recovered. In his passing, Germany lost one of the outstanding pediatricians of her period of medical greatness previous to the world war of 1914 to 1918.

In his teaching activities at Breslau, Strasbourg and Berlin, Professor Czerny influenced many Americans in their pediatric thinking and did much to give America her start in the development of pediatric clinics. It was my good fortune to work with him in Breslau and to visit him while he was active in Strasbourg and Berlin. I saw him for the last time during the fall of 1937, when he was in retirement at his Berlin home, after his return from Düsseldorf.

These periods of Czerny's life are of interest in that they represent three phases of his relationship to American pediatrics. His interest in the practice of pediatrics in this country was expressed to me one day early in 1908 in the clinic library at Breslau, when he said, pointing to his complete sets of the *Pediatrics* and the *Archives of Pediatrics:* "For years I have been reading your two national pediatric journals, and I have yet to find a contribution of value."

The great war intervened. Because of lack of funds many curtailments were made in the curriculums of German universities, and work in pediatrics was no exception. Again, I remember sitting with Professor Czerny, this time in the library of the Charité Pediatric Clinic, in 1927, when he remarked: "It is truly remarkable what you have accomplished in America during the past fifteen years; from almost nothing in 1908 you have developed to where you lead the world in pediatric thought and accomplishment."

In 1933 the *Journal of Pediatrics* issued a *Festschrift* in honor of Professor Czerny, which included publications from most of his former American pupils. In a letter Professor Czerny expressed his most grateful thanks and his great pride that, as evidenced by the contributions of his former students, he had had some share in the sudden and great growth of American pediatrics.

After his retirement as professor of pediatrics at the University of Berlin he was called to Düsseldorf to take over the work at the Düssel-

dorf Institute, the chair of pediatrics having been left vacant by the death of Professor Schlossmann. It was only the constant urging of the government that made him assume this extra burden at the advanced age of 73.

In 1937 Professor Czerny retired a second time and returned to his home in Berlin. On my visit in November of that year I found him well physically but very much perturbed about the future of the German universities. As he put it: "We have lost an entire generation in our universities, and perhaps they will never return to their former influence. No university can prosper when the truth is no longer searched for."

Professor Czerny was an inspiration for many American students of pediatrics. He was an outstanding figure in the field of nutrition and nutritional diseases of the infant and the child, and he was a pioneer in the study of mental health in childhood. A great man has gone.

H. F. H.

Abstracts from Current Literature

Anatomy and Embryology

THE DIFFERENTIAL MEASUREMENT OF SPEED IN PRIMARY SCHOOL CHILDREN. AILEEN CARPENTER, Child Development **12**:1 (March) 1941.

The study is concerned with the investigation of measurements of big muscle speed of children of the first, second and third grades. Records were obtained for 128 boys and 125 girls on the following events: right and left grips; broad jump; yard dash; fifty foot hop; three running events involving climbing over, climbing under and sitting by a "carpenter's horse" 2 feet (60 cm.) high; Sargent jump; baseball and volley ball throws for distance; baseball target throw; ball bounce, and ball catch. The events were intercorrelated separately for boys and for girls. Two factor analyses, one for each sex, were made according to Thurston's technic with rotations two at a time.

Strength and velocity factors were readily identified. By means of multiple regression technic, equations were derived for the prediction of strength and of velocity for boys and for girls of the primary grades.

The tests can be fitted into the program of physical education, can be used as objective means of measurement, and are recommended especially for use in research programs where long term investigations are under way.

AUTHOR'S SUMMARY.

DEVELOPMENT OF ROTARY-VESTIBULAR REACTIONS OF THE HUMAN INFANT. MYRTLE B. MCGRAW, Child Development **12**:17 (March) 1941.

A study was made on 67 infants, from birth to 2 years of age, of changing vestibular and ocular adjustments to bodily rotation. Characteristic changes in these adjustments were classified into three phases of developmental significance: A. Lateral deviation phase: In the newborn infant both head and eyes tend to deviate in the direction of rotation and to remain in the deviated position. B. Gross oscillatory phase: In the infant a few months old the face generally remains forward, but the eyes make gross, slow horizontal oscillations. C. Fine oscillatory phase: The older infant shows either fine rapid oscillations during rotation or no detectable response during rotation but equilibratory disturbance subsequently when placed on his feet. The shift from phase A to phase B in the greatest percentage of children occurs about the end of the fourth month and corresponds to the beginning of object vision. The onset of phase C occurs around the seventh month and corresponds to the beginning of equilibratory control in such activities as maintenance of a sitting posture. It becomes established about the end of the second year, which is also the time at which the child manifests optimum equilibratory control. It is considered doubtful that the cerebral cortex exercises much influence on these labyrinthine reflexes, and the development observed probably reflects maturation of the subcortical nuclei.

DAMMANN, Washington.

Metabolism; Infant Feeding; Milk and Other Foods

IRON BALANCES ON FOUR NORMAL PRE-SCHOOL CHILDREN. THELMA PORTER, J. Nutrition **21**:101 (Feb.) 1941.

Porter reports a study of 35 determinations of iron balance on 4 normal preschool children. These children, 3 to 5 years old, received a diet furnishing an average iron content of 5.64 mg., or 0.31 mg. per kilogram of body weight. The average

daily iron retention throughout the study of sixty-three days was 0.07 mg. per kilogram of body weight. An average of only 22 per cent of the total iron intake was stored by these growing children. With the replacement of 1 ounce (28 Gm.) of farina fortified with irradiated yeast containing 120 U. S. P. of vitamin D for the equivalent of plain farina in the basal diet, there was no significant effect on iron retention.

FREDEEN, Kansas City, Mo.

LIFE-TIME EXPERIMENTS UPON THE PROBLEM OF OPTIMAL CALCIUM INTAKE. F. O. VAN DUYNE, C. S. LANFORD, E. W. TOEPFER and H. C. SHERMAN. J. Nutrition **21**:221 (March) 1941.

F. O. Van Duyne and associates have shown by full life experiments with three generations of rats that a calcium intake of 0.64 to 0.8 per cent of the dry food used in the experiment gave optimal results in permanent nutritional well-being, even though the diet was suboptimal in riboflavin content and vitamin A.

FREDEEN, Kansas City, Mo.

DISORDERS OF NUTRITIVE DEFICIENCY AND THEIR TREATMENT. JAMES S. MCLESTER, New England J. Med. **224**:16 (Jan. 2) 1941.

The author describes verious types of nutritive deficiencies seen more frequently in the South than in the North. These include both preclinical and clinical pellagra. Symptoms of the former include nervous instability, changes in personality, mental depression, easy exhaustion, anorexia, vague digestive disorders, a tendency to diarrhea and a red tongue or a history of glossitis. Many patients with these symptoms have been previously considered "neurasthenics."

Other cases described are those of achlorhydria with diarrhea and anemia, which are often early pernicious anemia, and the digestive disorders and disabilities of old age often due to lack of protein, vitamins and minerals. In the treatment emphasis is placed on a well balanced diet and, when their use is indicated, the administration of additional vitamins and minerals well above the amounts considered optimal.

GENGENBACH, Denver.

CERTIFIED MILK—YESTERDAY AND TOMORROW. SAMUEL ADAMS COHEN, New York State J. Med. **40**:1317 (Sept. 1) 1940.

Certified milk is the only milk of choice for infants and "is destined to be the basis of the diet for all ages because it will incorporate all the nutritional needs of the people of its time."

AIKMAN, Rochester, N. Y.

Vitamins; Avitaminoses

FATE OF THIAMINE IN THE DIGESTIVE SECRETIONS. D. MELNICK, W. D. ROBINSON and H. FIELD JR., J. Biol. Chem. **138**:49 (March) 1941.

In previous studies the authors have observed that urinary excretion of thiamine is low after oral administration of test doses of thiamine hydrochloride to normal subjects in the postabsorptive fasting state, as well as during antacid ulcer therapy, when the amount of the excretion may at times fall within the deficiency range. They suggest that these low values may result from the destruction of thiamine in a gastrointestinal tract made unusually alkaline either by the powders used in therapy or by the suppression of gastric secretion in fasting.

In the present experiments, therefore, they study the stability of thiamine in vitro under conditions likely to be encountered in vivo. They find it very stable in normal gastric juice, even at high p_H, but note a loss of activity when antacids are added. There is a considerable loss of thiamine also in bile at its own p_H of 8; but acid bile destroys less thiamine. The results indicate that the maintenance of

acid secretions is important in the preservation of thiamine in the digestive tract. The authors suggest the probable ways in which activity is preserved in the normal human organism.

THOMAS, Chicago.

EFFECT OF A. T. 10 (DIHYDROTACHYSTEROL) ON RICKETS IN RATS PRODUCED BY HIGH-CALCIUM–LOW-PHOSPHORUS DIETS. ALFRED T. SHOHL and SIDNEY FARBER, J. Nutrition **21**:147 (Feb.) 1941.

Shohl and Farber concluded that A. T. 10 dihydrotachysterol in the dosage used, which approximated toxic dosage, protected rats from the development of rickets produced by a high calcium, low phosphorus ricketogenic diet. Dihydrotachysterol was five times as toxic and only one four-hundredth as effective as vitamin D in curing rickets. The serum calcium levels were definitely raised by dihydrotachysterol when the dose was increased to the point near which toxic symptoms appeared. The drug exerted its effect principally on excretion of phosphate in the urine, and to a lesser extent on the absorption of calcium.

FREDEEN, Kansas City, Mo.

RIBOFLAVIN CONTENTS OF SOME TYPICAL FRUITS. CAROLINE SHERMAN LANFORD, BEATRICE FINKELSTEIN and H. C. SHERMAN, J. Nutrition **21**:175 (Feb.) 1941.

The authors found that the citrus fruits (orange and grapefruit), banana and tomato appeared richer in riboflavin than the pome fruits (apple and pear). These results were the same whether the fruits were compared according to weight or according to caloric value.

FREDEEN, Kansas City, Mo.

THE DISTRIBUTION OF PANTOTHENIC ACID IN CERTAIN PRODUCTS OF NATURAL ORIGIN. THOMAS H. JUKES, J. Nutrition **21**:193 (Feb.) 1941.

The pantothenic acid contents of a number of foods as measured by biologic assay with chicks are presented in several tables.

FREDEEN, Kansas City, Mo.

THE EFFECT OF DIET ON THE PANTOTHENIC ACID CONTENT OF EGGS. ESMOND E. SNELL, ESTHER ALINE, J. RUSSELL COUCH and PAUL B. PEARSON, J. Nutrition **21**:201 (Feb.) 1941.

The authors conclude that the pantothenic acid content of the egg is directly dependent on the level of pantothenic acid in the diet of the hen.

FREDEEN, Kansas City, Mo.

CEREALS AND RICKETS: XIII. PHYTIC ACID, YEAST NUCLEIC ACID, SOYBEAN PHOSPHATIDES AND INORGANIC SALTS AS SOURCES OF PHOSPHORUS FOR BONE CALCIFICATION. CARL H. KRIEGER, RUDOLF BUNKFELDT, C. RAY THOMPSON and HARRY STEENBOCK, J. Nutrition **21**:213 (March) 1941.

These Wisconsin investigators found that the phosphorus of phytic acid is poorly available for the calcification of bone. This is in marked contrast to the readily available phosphorus of yeast nucleic acid and soybean phosphatides, which are as available as inorganic phosphorus. Even with the addition of vitamin D the utilization of the phosphorus of phytic acid, which in general is more utilizable than the other forms of phosphorus, was less efficient for calcification of bone than the other sources.

FREDEEN, Kansas City, Mo.

URINARY EXCRETION OF THIAMINE ON HIGH FAT AND HIGH CARBOHYDRATE DIETS. WILLIAM M. CAHILL, J. Nutrition **21**:411 (April) 1941.

Cahill reports that the urinary excretion of thiamine of adults was not significantly affected by either a high fat diet or a high carbohydrate diet.

FREDEEN, Kansas City, Mo.

RIBOFLAVIN CONTENT OF BLOOD AND MUSCLE IN NORMAL AND IN MALNOURISHED HUMANS. A. E. AXELROD, T. D. SPIES and C. A. ELVEHJEM, Proc. Soc. Exper. Biol. & Med. **46**:146 (Jan.) 1941.

In this study 5 cc. of venous blood was obtained from 35 patients with varying degrees of riboflavin deficiency and from 30 members of the laboratory staff. These patients had cheilosis and conjunctivitis; each one of them was relieved of his symptoms by the oral administration of riboflavin. Microbioassays using a specific strain of Lactobacillus casei for acid production revealed that no essential difference in the riboflavin content of the two groups of subjects existed. An average value of 0.42 micrograms of riboflavin per cubic centimeter was found in the 20 normal control subjects and 0.40 micrograms per cubic centimeter in the 35 patients with riboflavin deficiency. The same technic was used in a study of muscle tissue in a group of 30 patients with varying degrees of pellagra and 9 patients of normal nutrition. There was no essential difference in the riboflavin content of the tissues. Thus the determination of blood and muscle riboflavin is of no essential value in estimating the state of riboflavin deficiency in man.

HANSEN, Minneapolis.

CURE OF SIGNS OF "EGG WHITE" DISEASE BY CORN OIL, FATTY ACIDS AND VITAMIN B_6. EATON M. MACKAY and RICHARD H. BARNES, Proc. Soc. Exper. Biol. & Med. **46**:353 (Feb.) 1941.

Addition of corn oil (a source of unsaturated fatty acids) to the diets of rats suffering from "egg white" dermatitis considerably alleviated the symptoms. When vitamin B_6 (pyridoxine hydrochloride) was added to the corn oil, the symptoms of egg white acrodynia almost entirely disappeared.

HANSEN, Minneapolis.

OBSERVATIONS ON THE EFFECTIVENESS OF A YEAST–PEANUT BUTTER MIXTURE IN VITAMIN B COMPLEX DEFICIENCIES. T. D. SPIES, H. M. GRANT and J. M. GRANT, South. M. J. **34**:159 (Feb.) 1941.

The authors report that 23 patients with mild deficiency diseases improved after the daily ingestion of a yeast–peanut butter mixture.

Although yeast and the peanut both contain nicotinic acid, riboflavin and thiamine, the total effect of this supplement is not due to these vitamins alone, since per unit of weight this compound contains as much carbohydrate as potatoes, more protein than steak and one half as much fat as butter.

SCHLUTZ, Chicago.

HYPOTHROMBINEMIA AND VITAMIN K IN NUTRITIONAL DEFICIENCY STATES. E. D. WARNER, T. D. SPIES and C. A. OWEN, South. M. J. **34**:161 (Feb.) 1941.

The authors studied the prothrombin level in patients having pellagra and associated nutritional deficiency states. They believe that a deficiency of vitamin K is not common in conditions of this type.

Complicating factors, such as prolonged diarrhea, do at times, however, result in a serious deficiency of this vitamin.

Many chronically debilitated patients have a moderate hypoprothrombinemia, which apparently is due to causes other than a deficiency of vitamin K.

SCHLUTZ, Chicago.

"POT LIQUOR": A NEGLECTED SOURCE OF VITAMIN C FOR THE FEEDING OF INFANTS. M. L. KELLER and A. S. MINOT, South. M. J. **34**:163 (Feb.) 1941.

The authors believe that the old custom of feeding "pot liquor" to babies has some value, in that it furnishes fairly adequate amounts of vitamin C.

Although the requirements for this vitamin are now met with more desirable food supplements, it would be well to advise the retention of the old custom in instances in which the more conventional sources of vitamin C are unavailable.

SCHLUTZ, Chicago.

EXCRETION OF ASCORBIC ACID IN THE URINE OF SICK INFANTS. E. INGLESSI and A. AFENDAKI, Riv. di clin. pediat. **38**:715 (Dec.) 1940.

Determination was made of the ascorbic acid excretion in the urine of 65 infants under 2 years of age who were sick with measles, whooping cough, bronchopneumonia, diarrhea, nephritis or pyelocystitis. The excretion was found to diminish as illness progressed. The conclusion is drawn that more vitamin C is needed by and should be furnished for the child during illness.

HIGGINS, Boston.

BERIBERI WITH MENINGEAL SYMPTOMS IN A CHILD. GUSTAVO CARDELLE PENICHET and ARGELIO GARCIA LOPEZ, Arch. de med. inf. **10**:51 (Jan.Feb.-March) 1941.

In a 17 month old child there suddenly developed irritability, cyanosis, tachycardia and paralysis of the neck muscles. Administration of vitamin B_1 caused a disappearance of all these symptoms except the cyanosis, which yielded only to the administration of other factors of the vitamin B complex.

SANFORD, Chicago.

Hygiene; Growth and Nutrition; Public Health

CARE OF THE FEET OF NORMAL CHILDREN. HAROLD A. SOFIELD, Illinois M. J. **79**:253 (March) 1941.

The author summarizes his article as follows:

"1. Normal feet of children should not be restricted by stiff shoes.

"2. Low, flat heels or no heels at all on shoes are desirable for both boys and girls.

"3. The normal foot is benefited by barefoot exercise.

"4. Any deviation from the normal should be studied and treated by skilled physicians and surgeons.

"5. Feet cannot be considered separate parts of the body but must be viewed as important elements of the entire human mechanism." BARBOUR, Peoria, Ill.

BUILD VARIATIONS IN ADOLESCENT GIRLS. LEONA M. BAYER, J. Pediat. **17**:331 (Sept.) 1940.

The author cites a recent study of feminine build in relation to menstrual disorders and obesity, in which four types of feminine build are described. This paper is concerned with the question of whether the morphologic variations occurring in an essentially normal group of girls observed during the seven year study of growth known as the California Adolescent Study are such as to permit identification of these types. A classification of feminine build is described which seeks to sort persons according to the degree and direction of their secondary sex differentiations. It is based on a consideration of skeletal proportions and body covering. Two thirds of a group of normal adolescent girls could be fitted into the categories outlined—namely, hypofeminine (Diana), normal feminine (Venus), hyperfeminine (Rubens) and virile (Amazon). Girls of the normal feminine type have well developed breasts and body hair normally distributed. The sitting height–stature index (sitting height divided by stature) and the trunk breadth index (bicristal pelvic breadth divided by biacromial breadth) are within a percentage range of one standard deviation. The hypofeminine type includes those in whom the breasts are small, the hair sparse and both indexes small, signifying

long legs and a narrow pelvis. In the hyperfeminine type the breasts are large, the hair is dense and sometimes excessive and one or both indexes are large, signifying short legs and a broad pelvis. Girls of the virile type have small breasts and excessive hair; the sitting height–stature index is within the feminine and hyperfeminine range, but the pelvis is narrow and the shoulders are broad.

RAUH, Cincinnati.

WEIGHT AND MENSES IN ADOLESCENT GIRLS, WITH SPECIAL REFERENCE TO BUILD. LEONA M. BAYER, J. Pediat. **17**:345 (Sept.) 1940.

A series of 92 adolescent girls were studied with regard to certain aspects of weight, menstruation and build. Data on the age of menarche and on the menstrual cycle were found to be essentially similar to comparable data in the literature. Normal menstrual cycles for the group showed intervals of twenty to forty days with duration of flow from four to seven days. The mean menarcheal age was 13.16 years. The first year after the menarche showed great variability in length of cycle, but after the first two periods this variability was found to fall to a fairly uniform level. When the girls were sorted into build groups designated as hypofeminine, feminine, hyperfeminine and mixed, both weight and menstrual experience showed some relation to build. The following facts were noted: 1. When weight deviations occurred, the tendency was toward underweight among the hypofeminine girls and overweight among the hyperfeminine. 2. In the feminine group, (*a*) most of the girls reached their menarche within a very narrow range of the mean of 13.16 years, as against a much wider distribution in the others; (*b*) only 1 girl reported an interval between periods longer than sixty days or a period lasting longer than eleven days, as against six reporting such abnormal periods among the others; (*c*) only 1 girl reported severe dysmenorrhea, as against 5 among the others reporting such pain.

RAUH, Cincinnati.

A STUDY OF THE INCIDENCE OF ILLNESS AMONG INSTITUTIONAL CHILDREN. H. E. THELANDER, J. Pediat. **17**:367 (Sept.) 1940.

In order to determine the actual incidence of illness occurring in child-caring institutions, the records of four such institutions were analyzed. These records covered a period of three years and represent fairly accurately the amounts of routine work among well children, preventive work and care of the sick that are required for adequate medical supervision of children between the ages of 1 and 15 years. Thelander concludes from this analysis that an institution caring for 100 children should provide for a dispensary service accommodating approximately fifteen visits a day for five days a week. It should have an infirmary that would care for approximately 600 patients during the year. In addition to this medical work at the institution, there should be a close affiliation with a hospital for clinic consultations and for available beds when necessary. The clinic connection should, if necessary, provide for three hundred and fifty visits a year. Provision should also be made for between eighty and a hundred hospital days' care. On an average each child will be in bed six or seven days of the year, and over 50 per cent of the bed care will be for infections of the respiratory tract.

RAUH, Cincinnati.

THE SCHOOL PHYSICIAN IN THE PUBLIC HEALTH PROGRAM. GEORGE M. WHEATLEY, New York State J. Med. **40**:1507 (Oct. 15) 1940.

This article is part of a symposium on public health programs. Wheatley points out that the school physician is no longer a medical inspector; that he is, rather, a medical adviser who consults with the teacher, the nurse and the parents regarding the children. His work could be made to demonstrate the value of health examinations.

AIKMAN, Rochester, N. Y.

REPORT OF INTENSIVE LABORATORY STUDIES OF HIGH-SCHOOL ATHLETES. LEE S. PRESTON, New York State J. Med. **40**:1599 (Nov. 1) 1940.

Of specimens of urine obtained from 36 players immediately after football practice scrimmage, 6 were found to contain albumin. Casts, red blood cells and leukocytes were seen by microscopic examination. Further studies made during the season revealed an albumin content ranging from 0.5 to 6.0 per cent, with a mean average of 1.1 per cent. The content was consistently higher after scrimmage and games and was lower or absent after one or two days of rest. The abnormalities seem to have been of functional origin, for they disappeared in all but 1 patient at the end of the season. The boys were between the ages of 16 and 18 years. Preston wonders whether this condition may lead to further renal change when the boys reach full maturity.

AIKMAN, Rochester, N. Y.

THE SCHOOL PHYSICIAN AND THE CARE OF THE ATHLETE. ROBERT H. BROAD, New York State J. Med. **40**:1603 (Nov. 1) 1940.

The primary responsibility of the physical welfare of school athletes rests on the school physician. He should inform the physical instructor, the parents, the nurse, the teacher and the coach regarding the importance of proper physical examinations and prompt reports of illness. At least one thorough physical examination should be made each year, by one competent physician rather than a group of physicians. Whenever a defect is found, the student should be referred to a specialist. In addition to the annual examination, a check of the heart, the lungs and any previously injured parts and also a search for hernia should be made before each new sport. The school physician should also have supervision over the athletes to see that generally accepted hygienic rules are observed.

AIKMAN, Rochester, N. Y.

CHILD HEALTH: THE RESPONSIBILITY OF THE FAMILY PHYSICIAN AND THE PEDIATRICIAN. H. F. GARRISON, South. M. J. **34**:67 (Jan.) 1941.

The author stresses the importance of an increased amount of cooperation between the family physician and the pediatrician. The family physician should realize his inability to render specialized pediatric service. There should never be any hesitancy on his part to seek the advice of the pediatrician when that advice is needed.

The author states that the duty of the pediatrician and of the family physician is to bring forth a life endowed with good heritage, to preserve that life in health and to assist in molding that life in character for service. The future strength or weakness of national life and character depends on the extent to which physicians fulfil or neglect that duty.

SCHLUTZ, Chicago.

Prematurity and Congenital Deformities

A SURVEY OF CONGENITAL ANOMALIES AS FOUND IN 1,131 NECROPSIES. PETER GRUENWALD, Illinois M. J. **79**:55 (Jan.) 1941.

The author reviews 206 congenital anomalies observed in 1,131 necropsies at the Cook County Hospital.

BARBOUR, Peoria, Ill.

THE CARE OF THE PREMATURE INFANT. ETHEL C. DUNHAM and JESSIE M. BIERMAN, J. A. M. A. **115**:658 (Aug. 31) 1940.

The authors discuss the history of the progress in treatment of the premature infant. Even before the last half-century, regulation of body heat, prevention of infection and proper feeding were recognized as essential to good results.

The factors which have especially contributed to improved results have been breast feeding with improved maternal diet and organized community efforts to give widespread care to these infants. In 28 states there are organized plans to provide medical and nursing care, incubator service and other assistance, available to all.

The importance of this problem is shown by the fact that even in 1938 there were still 31,000 deaths in the United States attributed to prematurity. However, this figure represents a decrease of 7 per cent in the mortality rate as compared with that for 1935. HEERSMA, Kalamazoo, Mich.

CONGENITAL ANOMALIES OF THE PELVIC ADNEXA. JOSEPH D. FERRONE, New England J. Med. **224**:147 (Jan. 23) 1941.

Congenital anomalies are caused by errors in development. When the caudal ends of the apposed müllerian ducts fail to fuse, one sees all sorts of malformations, such as uterus didelphys, uterus arcuatus and uterus bicornis. Less often the cranial ends of the ducts fail to develop properly and other anomalies appear. Rudimentary tubes and ovaries are found, or the adnexa may be entirely absent. The tube may be a stub at the cornu of the uterus, and the ovary may be found anywhere in the pelvic cavity, posterior peritoneal wall, inguinal canal, labia majora or uterine wall.

An analysis of the records at the Newton Hospital from 1923 to the time of writing reveals that a diagnosis of double uterus was made in 2 cases, of bicornate uterus in 1 and of absence of the fallopian tube in 1.

The records of the Boston City Hospital were reviewed from 1915 to the time of writing, with the following results: The diagnosis of double uterus was made in 9 cases; that of bicornate uterus, in 7; that of septate (or double) vagina, in 5; and that of congenital anomaly of the tubes and ovaries, in 4.

All the cases of congenital anomaly of the adnexa that have been reported have been discovered accidentally or incidentally. GENGENBACH, Denver.

THE PREMATURE INFANT: A STATISTICAL STUDY. MARCUS B. EINHORN, New York State J. Med. **40**:1380 (Sept. 15) 1940.

A study of 204 premature infants is presented. An increase in breast feeding had a beneficial effect on the survival rate. It is recommended that a special room equipped for the care of premature infants be provided in maternity wards.

AIKMAN, Rochester, N. Y.

GARGOYLISM: A REVIEW OF THE PRINCIPAL FEATURES WITH A REPORT OF FIVE CASES. J. L. HENDERSON, Arch. Dis. Childhood **15**:201 (Dec.) 1940.

The author reviews 57 cases of gargoylism recorded in the literature and presents 5 additional cases. The disease is a form of congenital chondro-osteodystrophy in which the deformities of the head, trunk and limbs are associated with mental defect, corneal clouding and hepatosplenomegaly.

The most constant pathologic changes are found in the osseous and nervous systems. The bones are thickened, and many of them display characteristic deformities. In the brain there are widespread degenerative changes in the nerve cells, with intracellular and extracellular lipoid deposits. Lipoid deposits may occur in the corneas, the liver, the spleen and other tissues. The disease is recessively inherited, and there is a high familial incidence. There have been 5 instances of consanguinity in the parents. The available evidence, although fragmentary, offers a considerable amount of support for the view expressed by several authors within the last few years—namely, that the disease should be grouped with the congenital disorders of lipoid metabolism. KELLY, Milwaukee.

Newborn

PRIMARY VIRUS PNEUMONITIS WITH CYTOPLASMIC INCLUSION BODIES. JOHN M. ADAMS, J. A. M. A. **116**:925 (March 8) 1941.

This study of an epidemic involving 32 infants, 9 of whom died, may be summarized as follows: 1. Remarkably uniform symptoms of sneezing, coughing, dyspnea, cyanosis, listlessness and low grade fever were present. In many instances the cyanosis was intense and was accompanied by long periods of apnea and bradycardia. 2. Rather meager physical signs referable to pulmonary disease were elicited, a few scattered fine rales being the most consistent finding. 3. Roentgenologic studies disclosed evidence of patchy disturbances of bronchopneumonia. 4. Bacteriologic studies revealed no uniformity in bacteria found in patients or contacts. 5. Pathologic examination made in all the lethal cases disclosed pneumonitis, atelectasis and peribronchial infiltration with sloughing of bronchial epithelium. 6. Remarkable demonstrations were made of cytoplasmic inclusion bodies in the bronchial epithelium of all 9 patients who died.

The author could find no description of previous epidemics in small infants presenting the clinical and pathologic picture encountered. This appears to be the first time that cytoplasmic inclusion bodies have been demonstrated in the bronchial epithelium of human subjects in association with a uniform clinical syndrome.

HANSEN, Minneapolis.

STUDIES ON THE BLEEDING TENDENCY AND VITAMIN K THERAPY IN NEWBORN CHILDREN. HENRY LEIDENHEIMER JR. and ANDREW STIRLING ALBRITTON, New Orleans M. & S. J. **93**:464 (March) 1941.

The authors report observations on 5 cases of frank hemorrhagic disease of the newborn. Four were studied by the bedside test of Ziffren and associates and 1 by the Boyce serum volume index. All the patients except 1 were treated without appreciable effect by the usual methods of transfusion or intramuscular injection of blood. All promptly responded to the use of vitamin K and were discharged well.

Using chiefly the serum volume index, the authors made 450 tests on 41 mothers and 111 children. They discovered no perceptible change in the blood values in infants born of mothers treated ante partum with vitamin K, but they found that 1 mg. administered to the newborn infants nearly eliminated the usual fall on the third day of life. Doses of 2 mg. resulted in rising values, which reached those of the normal adult at the fifth day.

The authors agree with Waddell and Guerry in their suggestion that newborn infants should not be subjected to surgical procedures without the previous administration of vitamin K.

On the basis of their work the authors believe that fatalities from hemorrhagic disease should be reduced to a negligible figure by the use of vitamin K and that the disease should be considered as due to this specific deficiency.

BERKLEY, Los Angeles.

STUDY OF THE SERUM LIPIDS IN SCLEREMA NEONATORUM. LUIGI LUZZATTI and ARILD E. HANSEN, Proc. Soc. Exper. Biol. & Med. **46**:325 (Feb.) 1941.

Study of the subcutaneous fat tissue and of the serum lipids of a 3½ month old, breast-fed girl with sclerema neonatorum was made, both at the time the disease was manifest and when all evidence of the disorder had disappeared. It was believed that this approach to the problem might help to provide a better understanding of the nature of the disturbance and might also help in detecting any evidence of a metabolic abnormality which may be associated with this condition. The histologic appearance and the chemical structure of this tissue revealed the known alterations: chronic inflammatory reaction and presence of abnormal amounts of saturated fatty acids (iodine number, 42). When the condition was improved, repeated analyses revealed normal adipose tissue, both histo-

logically and chemically (iodine number, 57). Early in the disease an increase in all the fractions of the serum lipids was present; associated with this was a decrease in the iodine number, especially of the neutral fat. When all signs of the disease had disappeared, the blood lipids were normal. Fat absorption as shown by balance studies and by blood studies was within normal limits. The lipemia is discussed briefly in the light of the alterations of the fat tissue, and it is suggested that a disturbance in the deposition of fat or in its transportation from the pathologic areas may be present in this disease. The clinical observation gives support to the idea that this tissue was metabolically altered.

HANSEN, Minneapolis.

OMPHALOCELE CONGENITUM HEALED BY A NEW CONSERVATIVE PROCEDURE. S. BLAZSÓ, Orvosi hetil. **84**:269 (May 25) 1940.

Hernia into the umbilical cord requires surgical intervention immediately after birth, for the prognosis of a later operation is much worse. Blazsó observed a 4 day old infant with a defect on the abdominal wall the size of a hand, covered with dry amniotic membrane with beginning suppuration of its margin. He constructed a new instrument, consisting essentially of two steel tracks between which the empty sac was pressed (the intestines having been pressed out of it beforehand). The amniotic membrane came off in ten days and the wound healed in one month.

GÖTTCHE, Budapest.

THE BIRTH WEIGHT OF FULL TERM CANTONESE BABIES. K. H. UTTLEY, Chinese M. J. **58**:582 (Nov.) 1940.

This physician, a medical officer of Hong Kong, records the first large series of weights of newborn infants from the Civil Hospital in Kowloon. The total of 5,437 included a few more boys than girls. The weight occurring with the greatest frequency among the boys was 6.5 pounds (2,948 Gm.); that among the girls was 6.0 pounds (2,722 Gm.). The averages of all weights were 6.7 pounds (4,627 Gm.) and 6.5 pounds (2,948 Gm.) respectively.

There was a slight tendency of babies born at successive pregnancies to be heavier up to the seventh pregnancy. The incidence of twins was 15.6 per thousand deliveries; the individual twin averaged 1¼ to 1½ pounds (565 to 680 Gm.) less than the single birth. These weights compare about equally with those in reports of Peiping infants but are somewhat lower than those of newborn infants in other portions of China.

NEFF, Kansas City, Mo.

Acute Contagious Diseases

SULFANILAMIDE AND CONVALESCENT SERUM IN SCARLET FEVER. ALBERT M. WOLF and SIDNEY O. LEVINSON, Illinois M. J. **79**:239 (March) 1941.

From a review of the literature and a clinical study, the authors conclude that sulfanilamide does not produce amelioration of the initial acute symptoms of scarlet fever. In their series the routine use of sulfanilamide during the first week of the disease as an adjunct to convalescent serum therapy did not decrease the incidence of subsequent complications more than did the serum therapy alone.

BARBOUR, Peoria, Ill.

SULFAPYRIDINE IN MENINGOCOCCIC MENINGITIS: REVIEW OF THE LITERATURE AND REPORT OF A CASE. HERMAN I. KANTOR, New York State J. Med. **40**:1526 (Oct. 15) 1940.

A woman aged 66 was admitted to Mount Sinai Hospital, New York, Oct. 10, 1939, in a semiconscious condition. The temperature was 103 F. The respiration was stertorous. The face was flushed and somewhat drawn. There was rigidity of the neck, which was painful on forced flexion. Spinal tap showed cloudy fluid

under pressure. The sugar content was 40 mg. per hundred cubic centimeters. A twenty-four hour culture revealed a pure growth of meningococcus. The leukocyte count was 15,800 cells per cubic millimeter, with 93 per cent polymorphonuclears. There was a marked shift to the left. The following routine was adopted: (1) slow intravenous infusion of 5 per cent dextrose in distilled water, with 20 cc. of antimeningococcus serum added every four hours; (2) spinal taps every eight hours for drainage and for the introduction of antimeningococcic serum; (3) sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) in suspension given through a Levine tube into the stomach, with the patient under an oxygen tent; (4) supportive symptomatic therapy as indicated. By the evening of the second day of her illness, the patient was conscious and rational and her temperature was normal. Then nausea appeared, and the administration of sulfapyridine was stopped. The patient became worse, and pneumonia of the upper lobe of the left lung was diagnosed. Sulfapyridine was then given despite the grave condition, and on the fifth day improvement began and continued to recovery. Kantor attributes the successful outcome to sulfapyridine, which has been much used in the treatment of epidemic meningitis abroad but not very widely in the United States.

VOORHEES, New York. [ARCH. OTOLARYNG.]

PREVALENCE OF POLIOMYELITIS IN THE UNITED STATES IN 1940. C. C. DAUER, Pub. Health Rep. **56**:875 (April 25) 1941.

In 1940 the incidence of poliomyelitis increased 30 per cent over that in 1939. There was a total of 9,770 cases. The year was characterized by epidemics in several large areas of the north central section and of the northern Rocky Mountain section. This article contains considerable detailed information about the various sections and is accompanied by a spot map of the incidence in the United States. It should be read in detail by any one interested in this problem.

SANFORD, Chicago.

TREATMENT OF MENINGOCOCCIC MENINGITIS. DE LA B. FORTIER, Union méd. du Canada **69**:586 (June) 1940.

Fortier presents two cases of meningococcic meningitis with recovery. One child received antimeningococcus serum fourteen days after the onset of his illness. Improvement was prompt, but a relapse occurred three weeks later. He was given more serum, together with "prontosil" (preparation not further identified), and recovery was uneventful. The other child received only chemotherapy—a combination of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), sodium sulfapyridine and azosulfamide (neoprontosil; disodium-4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′, 6′-disulfonate).

DAFFINEE, Boston.

POLIOMYELITIS: IV. THE SPREAD OF POLIOMYELITIS VIRUS IN CYNOMOLGUS MONKEYS WITH PARTICULAR REFERENCE TO INFECTION BY THE PHARYNGEAL-INTESTINAL ROUTE. F. M. BURNET and A. V. JACKSON, Australian J. Exper. Biol. & M. Sc. **18**:361 (Dec.) 1940.

Using a locally isolated strain ("Mar") of poliomyelitis virus, infection of the central nervous system was produced by intradermal inoculation in 6 of 9 cynomolgus monkeys and in 5 of 14 rhesus monkeys. The same procedure with Rockefeller Institute mixed virus ("M. V.") in 6 cynomolgus monkeys was not followed by paralysis in any of the animals. After intracerebral infection with either "Mar" or "M. V.," virus was isolated from peripheral nerves in cynomolgus monkeys only. Infection was produced in cynomolgus monkeys by intraperitoneal inoculation, the infection in 2 instances inducing a high grade of immunity. Oral administration of the virus strain "Mar" to 7 cynomolgus monkeys was followed by typical infections in 5 of the animals. The results of tests for virus in nerves, lymph nodes and other tissues from these animals suggest that primary multiplication occurs in the pharynx and in the intestine and that the spread of the organism

to the central nervous system takes place by the autonomic nerves. A single experiment in which apparent multiplication of the strain "Mar" took place in pharyngeal and intestinal tissues from a human fetus is taken as presumptive evidence that one strain at least of poliomyelitis virus is capable of infecting non-neural tissues.

GONCE, Madison, Wis.

ACUTE POLIOMYELITIS. W. HOWLETT KELLEHER, Brit. J. Child. Dis. **37**:217 (Oct.-Dec.) 1940.

This report covers 35 cases of poliomyelitis studied in the Western Hospital of London in 1937 and 47 cases studied in 1938. The patients ranged in age from 1 year to 34 years, the majority falling into the 5 to 10 year age group. In 23 instances the paralysis set in within twenty-four hours of the onset of the first symptom. Only 6 patients were admitted to the hospital as early as the second day of illness.

The lack of recovery of the intercostal muscles in all the patients for whom a respirator had been used was a disturbing feature and rendered the ultimate prognosis extremely poor for even partial recovery.

Convalescent serum was not used.

A thorough discussion of treatment in respirators (Siebe-Gorman and Both) is included.

LANGMANN, New York.

IMMUNIZATION AGAINST DIPHTHERIA. Edinburgh M. J. **48**:126 (Feb.) 1941.

Under 8 years of age nearly all children are susceptible to diphtheria, as is shown by the Schick reaction. This would seem to make it unnecessary to make routine tests of children of that age group. After the age of 8 years the test is invaluable, for many are immune and can be spared the immunization procedures, which are at that age likely to be accompanied by reactions. It is preferable to begin immunization at the age of one year and to confine the efforts to protecting the child during the preschool period, during which he is most susceptible.

For young children the author recommends two injections of alum-precipitated toxoid, a month apart, with periodic Schick tests in the following years of childhood. Toxoid-antitoxin floccules are desirable for use in immunizing children over 8 years of age, for they cause no objectionable reaction.

Diphtheria is still a problem in Scotland, where there is an average of 10,000 cases a year, with about 400 deaths. The Scientific Advisory Committee appeals to the members of the medical profession to immunize at least 75 per cent of the child population and so bring Scotland into line with other countries.

NEFF, Kansas City, Mo.

CHEMOTHERAPY OF CEREBROSPINAL FEVER IN CHILDHOOD. MARGARET I. WILLIAMS, Lancet **2**:642 (Nov. 23) 1940.

Sulfanilamide (by mouth) alone was given to 94 patients, the average daily dose varying from 2.5 Gm. for infants to 7 Gm. for older children; the usual period of treatment was ten days. In 3 cases sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given alone and in 5 cases combined with sulfanilamide.

Age and Case-Fatality Rate

Age, Years	Cases	Deaths	Case-Fatality Rate, per Cent
0-1	21	4	19
1-2	17	3	17.6
2-5	30	4	13.3
5-10	16	0	0
10-15	18	2	11.1
Total	102	13	12.7

On admission of each patient, a lumbar puncture was performed. If the spinal fluid was turbid, sulfanilamide was given immediately. A second lumbar puncture was performed after twenty-four hours' treatment. The fluid was cultured and the sulfanilamide content estimated; if this was adequate (over 5 mg. per hundred cubic centimeters) and the fluid was sterile, no more lumbar punctures were done until the tenth day.

In 79 (77.4 per cent) of the 102 cases the meningococci cultured from the spinal fluid fell into group I; in 17 (16.7 per cent) they fell into group II. In 2 cases the group was not determined, as the strains agglutinated well with both group serums; and in 4 the strains were not typed. LANGMANN, New York.

LEUCOCYTE COUNT IN RUBELLA. MARTIN HYNES, Lancet **2**:679 (Nov. 30) 1940.

Serial leukocyte counts were performed on 61 adults with rubella.

Leukopenia was the rule at the onset, with the leukocyte count rising to the upper limit of normal by the tenth day.

At the onset half the patients had an absolute neutropenia. Gradually this became corrected, and after the tenth day a third of the patients had an absolute neutrophil leukocytosis.

There was an absolute lymphopenia at the onset but an absolute lymphocytosis after the fifth day.

Türck cells were always present and commonly numerous. They reached their maximum about the fourth day.

The erythrocyte sedimentation rate was usually normal.

LANGMANN, New York.

A CLINICAL SURVEY OF NINE CASES OF ENCEPHALOMYELITIS IN ASSOCIATION WITH MEASLES. M. E. CHINNER, M. J. Australia **2**:526 (Nov. 23) 1940.

During the 1939-1940 epidemic of measles in South Australia, Chinner observed 9 cases of encephalomyelitis. The average time of onset of nervous symptoms was four days after the appearance of the rash. In 4 instances the initial infection had been severe. At the time of the onset of the cerebral disorder the temperature in every case had been normal or had fallen considerably from its previous high level. In the fatal cases hyperpyrexia appeared before death. As initial symptoms, drowsiness occurred in 5 cases, vomiting was prominent in 4 and convulsions or muscular twitchings occurred in 3. Eventually stupor developed in all cases. In 6 cases there was either mild head retraction or much stiffness of the neck. The reflexes were variable, as was tonus of the limbs. Blindness of the cortical type occurred in 2 cases. The cells of the cerebrospinal fluid were usually increased in number, and lymphocytes predominated. In every instance there was considerable increase in globulin content. Death ensued in 3 cases; complete recovery occurred in 3 others. Of the 3 patients having sequelae, 2 had both mental and physical changes, and 1 had physical changes only, in the form of weakness and atrophy of muscle groups. GONCE, Madison, Wis.

INVOLVEMENT OF THE OPTIC NERVE IN ENCEPHALOMYELITIS FOLLOWING VACCINATION: REPORT OF CASES. F. VON HERRENSCHWAND, Klin. Monatsbl. f. Augenh. **102**:815 (June) 1939.

This paper was prompted by Scheyhing's publication of a case of optic neuritis with transient blindness associated with meningoencephalitis following vaccination for smallpox. The author describes 3 cases of his own. The patients were boys aged 7, 7 and 8 years respectively. The autopsy reports, illustrated by photomicrographs, are added. In all but 1 case the ocular disease was limited to the dural sheath of the optic nerve, sparing this nerve and also the septums between the bundles of its fibers. The process was secondary, in the author's opinion, descending from the meninges. In the optic nerve of 1 patient there were small foci resembling those found in the white cerebral substance in cases of encephalo-

myelitis following vaccination. This type of retrobulbar neuritis occurs, furthermore, in association with multiple sclerosis and lethargic encephalitis.

A point of histologic differentiation from these diseases, however, is the fact that in cases of encephalitis following vaccination glial proliferations forming continuous seams around the veins predominate. K. L. STOLL. [ARCH. OPHTH.]

EXPERIMENTAL PRODUCTION AND TREATMENT OF C. DIPHTHERIAE SINUSITIS IN RABBITS. C. Y. CHEN and T. T'UNG, Chinese M. J. **58**:649 (Dec.) 1940.

The authors conclude that the introduction of Corynebacterium diphtheriae causes an acute infection of the soft tissue lining of the sinus and produces a pathologic picture resembling that of diphtheria in man. The animal afterward becomes a carrier of C. diphtheriae. Animals may be made resistant to infection and to the carrier state by active immunization with diphtheria toxoid.

NEFF, Kansas City, Mo.

Acute Infectious Diseases

IRRIGATIONS WITH SULFANILAMIDE AS A TREATMENT FOR GONORRHEAL CONJUNCTIVITIS. W. J. REIN and O. B. TIBBETTS, Am. J. Ophth. **22**:1127, 1939.

Rein and Tibbetts examine all patients with conjunctivitis bacteriologically, and if gram-negative intracellular diplococci are found the patient is classed as having gonorrheal ophthalmia and is admitted to the hospital. The eye is irrigated every fifteen minutes night and day with a 0.5 per cent solution of sulfanilamide made up in physiologic solution of sodium chloride. If other complications exist (vaginitis or urethritis), the patients are given 30 to 60 grains (1.8 to 3,6 Gm.) of sulfanilamide orally. The following summary is given:

"1. A series of 15 cases of gonorrheal ophthalmia have been reported. We believe a new technique in the local use of sulfanilamide has been advanced.

"2. We feel that the local use of sulfanilamide in solution in the treatment of gonorrheal ophthalmia practically eliminates the danger of systemic reactions.

"3. In our series of 15 cases of gonorrheal ophthalmia treated locally with sulfanilamide there have been no ocular complications.

"4. The economic advantages, by reason of the reduction of the period of hospitalization to less than one third that required by use of other standard measures, are obvious.

W. S. REESE. [ARCH. OPHTH.]

ENTEROBIASIS: ITS INCIDENCE AND SYMPTOMATOLOGY IN A GROUP OF 505 CHILDREN. THOMAS H. WELLER and CHARLES W. SORENSON, New England J. Med. **224**:143 (Jan. 23) 1941.

A study of the incidence of enterobiasis was made on a group of 505 white patients from 2 to 12 years of age at the Children's Hospital in Boston. These children were divided into two groups: 118 patients studied in the medical wards and 387 patients examined in the Medical Outpatient Department.

Determination of the presence of pinworm infection was made by using the cellophane-tipped anal swab devised by Hall, generally known as the "NIH swab." Since the female pinworm lays its eggs on the perianal skin, this is the obvious site from which to recover eggs for diagnostic purposes.

Swabs were taken between 9:00 a. m. and 5:30 p. m. and examined on the same day. In no case were they taken before the morning toilet—a fact that must be considered in evaluating the results.

Of the entire group of 505 children examined, 97 (19 per cent) were found to have enterobiasis. Of the 387 outpatients, 42 (11 per cent) gave a history of previous pinworm infection. Examination of the swabs of 16 (38 per cent) of these gave positive results. Of the 345 outpatients with no history of infection, 56 (16 per cent) had positive results. Of 90 children from whom swabs were taken

a second time, 23 (26 per cent) were found to have ova. None of the patients with ova had an eosinophil count of more than 5 per cent.

In the present series, 23 per cent of the girls were infected, as compared with 15 per cent of the boys. Thirteen per cent of those from 2 to 4 years old, 23 per cent of those from 5 to 9, and 20 per cent of those from 10 to 12 were infected.

This study indicates that subclinical enterobiasis is a common condition. Such a conclusion seems to be adequately substantiated by the fact that of the 72 patients in whom the presence of ova was shown, 64 per cent had no gastrointestinal symptoms, 80 per cent had no perineal symptoms, 58 per cent had no nervous symptoms and 36 per cent had none of the three types of symptoms.

A significant difference was found between the average number of children under 14 years of age (3.1) in the families of the infected children and that (2.2) in the families of the uninfected children. GENGENBACH, Denver.

STAPHYLOCOCCUS AUREUS SEPTICEMIA. O. W. H. MITCHELL and O. D. CHAPMAN, New York State J. Med. **40**:1308 (Sept. 1) 1940.

A series of 38 cases in which blood cultures yielded Staphylococcus aureus is reported. Osteomyelitis was present in 18 patients, 15 of whom were children. Six of the 15 children died. All this occurred before the introduction of sulfathiazole.

AIKMAN, Rochester, N. Y.

AN OUTBREAK OF TYPHOID FEVER ASSOCIATED WITH A TRAILER CAMP. PAUL A. LEMBCKE and PHILIP J. RAFLE, New York State J. Med. **40**:1371 (Sept. 15) 1940.

In August 1938, 18 cases of typhoid fever were traced to a trailer camp near Oswego, New York. The permanent residences of the patients included seven different states. Members of the group had visited six places in the state of New York and one in Pennsylvania. The history of these cases shows the extent of the problem of infections in automobile tourist camps.

AIKMAN, Rochester, N. Y.

FREQUENCY OF INTESTINAL PARASITES IN CHILDREN IN THE CITY OF ATHENS. E. INGLESSI, Riv. di clin. pediat. **38**:685 (Nov.) 1940.

Of 4,330 children between the ages of a few days and 15 years seen in a pediatric outpatient department during a period of seventeen months, 368, or 8.4 per cent, had intestinal parasites. In 302 cases the parasites were worms—pinworms in 258, ascarids in 35 and tapeworms in 10. There were protozoal parasites in 62 cases—Amoeba histolytica in 27, Lamblia intestinalis in 28 and Trichomonas intestinalis in 7. There were 16 cases of infestation by two parasites and 3 cases of infestation by three parasites.

HIGGINS, Boston.

Chronic Infectious Diseases

TREATMENT OF CRYPTORCHIDISM WITH CHORIONIC GONADOTROPIC HORMONE AND MALE SEX HORMONE [ANDROGEN]. CARL ZELSON and ERNST STEINITZ, J. Pediat. **17**:315 (Sept.) 1940.

Seventeen boys with cryptorchidism ranging in age from 7½ to 12½ years, in 2 of whom the cryptorchidism was bilateral, received a course of combined treatment with injections of chorionic gonadotropin (pregnyl) and testosterone propionate. Each injection consisted of 500 rat units of gonadotropin with 5 to 10 mg. of testosterone propionate. Nine (53 per cent) of the boys responded with complete descent of the testes. These included 4 of 9 boys who had been treated with either preparation alone or with the two successively without any effect and 5 of 8 boys who had not been treated previously. Zelson and Steinitz recommended the following treatment for cryptorchidism: First, a course of treatment with

chorionic gonadotropin, in amounts from 300 to 500 rat units three times a week up to a total of 10,000 units. If no response results, a combined course of treatment with chorionic gonadotropin and androgen should be given. If the results remain unsatisfactory, the cryptorchidism should be treated surgically. Treatment should be instituted between the ages of 8 and 10 years. RAUH, Cincinnati.

CONGENITAL SYPHILIS IN ONLY ONE OF TWINS. F. R. SMITH JR. and J. M. SPENCE JR., South. M. J. **34**:147 (Feb.) 1941.

The authors cite 12 previously reported cases of congenital syphilis occurring in only one of twins. Of these, 5 were completely acceptable; the others, while probably authentic, suffered from lack of documentation of important detail. They present the criteria which must be fulfilled before the diagnosis of congenital syphilis in only one of twins may be made.

The authors then report 5 instances, from their own practice and from the records of Johns Hopkins Hospital, in which congenital syphilis occurred in only one of twins. They point out that since 4 of the 5 instances of this phenomenon were observed in 44 twin pregnancies to 40 women with syphilis, the condition is not so rare as might be expected. SCHLUTZ, Chicago.

JUVENILE PARESIS [DEMENTIA PARALYTICA] IN ONE TWIN. REDVERS IRONSIDE, J. Neurol. & Psychiat. **3**:329 (Oct.) 1940.

Ironside reports a case of juvenile dementia paralytica in one member of dizygotic twins, the syphilitic infection having been transmitted by the mother. The affected twin showed no stigmas of congenital syphilis except for general physical and mental retardation. When he reached the age of 10, he began to show signs of physical deterioration and the Wassermann reaction of the blood was positive. From the age of 15 there was progressive mental deterioration, characterized by childishness, irritability and impairment of memory, speech and intellectual processes. Neurologic examination at the age of 17 disclosed ataxia, dysarthria, tremor, and a Babinski sign bilaterally, and examination of the cerebrospinal fluid showed changes characteristic of dementia paralytica. The healthy twin appeared normal on clinical and serologic examinations. The literature contains only 2 other reports of similar instances, 1 of a dizygotic twin reported by Wile and Welton and 1 of a possibly monozygotic twin reported by McKendree. The explanation for the escape from infection of the healthy twin remains unknown.

MALAMUD, Ann Arbor, Mich. [ARCH. NEUROL. & PSYCHIAT.]

FALSE POSITIVE SYPHILITIS REACTIONS IN CHILDREN WITH TUBERCULOSIS. ANTONIO SELLEK AZZI and ALEJANDRO DEL FRADE, Arch. de med. inf. **10**:61 (Jan.-Feb.-March) 1941.

In a résumé of 100 instances the authors conclude that 5 per cent of children with tuberculosis will show falsely positive reactions for syphilis. The proportions were Kahn 4 per cent, Meincke 3 per cent and Sellek-Frade 2.6 per cent.

SANFORD, Chicago.

PETRAGNANI'S ANATUBERCULIN AS A DIAGNOSTIC AGENT. P. CAPPELLI, Riv. di clin. pediat. **38**:705 (Dec.) 1940.

Intradermal injection of anatuberculin of Petragnani by the Mantoux method is a much more sensitive diagnostic test than similar administration of bovine or human tuberculin. HIGGINS, Boston.

TUBERCULOSIS OF THE CONJUNCTIVA. N. K. IVANOV, Vestnik oftal. **14**:24, 1939.

Since tuberculosis of the conjunctiva is rare, 3 cases of this condition, of varying clinical courses, are reported. The patients were girls aged 12, 14 and 15 years respectively.

In 1 case the primary lesion of tuberculosis was diagnosed as a chalazion, but later it took the course of a typical tuberculous ulcer, with enlargement of the regional glands. In the second case tuberculosis of the conjunctiva was metastatic, with no enlargement of the glands; its course was torpid, and the lesions resembled the follicles of trachoma. In the third case, in which the involvement was severe, the lesion resembled a tumor of the conjunctiva, but histologic examination revealed its tuberculous character. It had spread from the nasal and oral cavities to the conjunctiva. The course was progressive, the conjunctival lesion spreading to the cornea. There was much granulation tissue. The final result was atrophy of the eyeball. In the first case therapy for tuberculosis gave good results, while in the other cases roentgen therapy was used with no effective results.

Ivanov discusses the ways of infection and the clinical picture of tuberculosis of the conjunctiva. He believes that the variety of the clinical forms of tuberculosis of the conjunctiva can be explained by different reactions of the organism to the tubercle bacilli, by the different immunobiologic conditions and by the stage of the inflammatory process.

O. Sitchevska. [Arch. Ophth.]

The Incidence of Tuberculous Infection in a Peiping Children's Clinic. Theresa T. Woo, Chinese M. J. **58**:671 (Dec.) 1940.

While mass tuberculin tests of all children still remains to be done in China, tests have been routinely made on all children attending the pediatric outpatient department of Peiping Union Medical College Hospital during the last five and one-half years. Most of the 4,776 infants and children on whom the tests were performed came from the poor or middle classes.

The incidence of positive reactions increased with age, ranging from 12.8 per cent for those tested in their first year of life to 80.7 by the time the twelfth year was reached.

Neff, Kansas City, Mo.

A Case of Blood Transfusion Syphilis. T. Ohno, Lues: Bull. Soc. japon. de syph. (Abstr. Sect.) **18**:19 (Aug.) 1939.

The author reports the case of a 1 year old infant in whom syphilis developed after the intramuscular transfusion of blood from the mother. One month after this transfusion there appeared in the infant at the site of injection a primary sclerotic lesion, followed by a large papule near the chancre and numerous small papules around the anus. Seventeen days before the examination of the child, the mother had had a generalized papular eruption and a strongly positive Wassermann reaction.

The author reviews 10 cases of blood transfusion syphilis recorded in the Japanese literature. In these cases the infection manifested itself from the start in secondary symptoms. More severe symptoms, such as fever, psoriasiform and pustular eruptions, crusted papules, petechiae, ulcers, visual disturbance and disturbance of motility of the extremities, are seen with blood transfusion syphilis more frequently than with ordinary syphilis.

Bloom, New York. [Arch. Dermat. & Syph.]

Diseases of Blood, Heart and Blood Vessels and Spleen

Plasma Prothrombin; Vitamin K. K. M. Brinkhous, Medicine **19**:329 (Sept.) 1940.

The author summarizes the recent developments which relate to prothrombin and to vitamin K. He states that most authorities agree that blood clotting is a two stage process:

1. Prothrombin plus calcium plus thromboplastin → thrombin.
2. Thrombin plus fibrinogen → fibrin (clot).

Recent experiments seem to prove that the conversion of prothrombin to thrombin is due to chemical union with calcium and thromboplastin and that the latter do not act merely as catalysts. The speed of the first step in clotting depends on the amounts of the three factors present, and also on the electrolyte concentration, on p_H (7 being the optimum p_H) and on temperature. Other factors may be species convertibility of the prothrombin and the amounts of coagulation-inhibitory factor present.

The author discusses the accuracy of the various clinical tests for prothrombin activity. Methods for the isolation of prothrombin are described. The amount in normal human plasma is about 300 units per cubic centimeter; this is about twice the amount necessary to prevent development of a hemorrhagic tendency. Accumulated data indicate that plasma prothrombin originates in the liver.

The chemistry of vitamin K is discussed. Vitamin K_1 has been shown to be 2-methyl-3-phytyl-1, 4-naphthoquinone. Vitamin K_2, which has about 60 per cent of the potency of K_1, has been isolated but not fully identified structurally. Phthiocol, which usually is obtained as a synthetic compound but also occurs naturally in tubercle bacilli and which is slightly soluble in water, might be designated as vitamin K_3. Many other compounds have vitamin-K-like activity.

Alfalfa, spinach and many green leafy vegetables are high in natural vitamin K. Bacteria likewise contain vitamin K. It appears that animals are unable to synthesize the vitamin except by bacterial growth in the intestine.

Simple dietary deficiency may cause prolonged clotting time in chicks and other fowls, in some rabbits, mice and rats. Four human beings whose dietary deficiency of vitamin K has led to prolongation of coagulation time have been reported. Liver damage *per se* causes hypoprothrombinemia and a hemorrhagic tendency which is not corrected by vitamin K and bile salts unless there is an associated deficiency of vitamin K. In patients with obstructive jaundice and biliary fistula the low prothrombin level and the hemorrhagic tendency are due to defective absorption of vitamin K from the intestine in the absence of bile; this is corrected by oral administrations of bile salts and vitamin K. Some preparations are effective when given parenterally.

Studies on the newborn show a smaller amount of plasma prothrombin in normal infants than in adults, and a marked fall between the first and the sixth day of life. In 15 cases of hemorrhagic disease of the newborn which have been studied the prothrombin time was increased; in 5 of these cases, vitamin K was administered, bleeding ceased and the hypoprothrombinemia was corrected. The reason for vitamin K deficiency and the spontaneous recovery in the newborn has not been found experimentally. Quick and Grossman suggest that recovery may be due to the development of a normal bacterial flora in the intestinal tract.

Hemorrhagic sweet clover disease of animals, although characterized by low prothrombin levels, is apparently not due to vitamin K deficiency. Sprue and other intestinal conditions are sometimes associated with a vitamin K deficiency. The occasional hemorrhagic tendency following artificial hyperpyrexia is apparently not due to hypoprothrombinemia alone. Patients with erythroblastosis foetalis have been treated with vitamin K_1 apparently with some success.

LIMPER, Louisville, Ky.

FAMILIAL HEMOLYTIC CRISIS—REPORT OF THREE CASES OCCURRING WITHIN TEN DAYS. WILLIAM DAMESHEK, New England J. Med. **224**:52 (Jan. 9) 1941.

Within a period of ten days, 3 children in the same household—2 brothers and a cousin—became successively ill. Each child was found to be suffering from a severe hemolytic crisis, and splenectomies were performed on all 3. The first child died, but the other 2 made uneventful recoveries.

The grandfather of the 3 children was known to have congenital hemolytic icterus. The father of the boys had been jaundiced since childhood. All of the children had had hemolytic crises. The spleen was enlarged, and the blood showed reticulocytosis, spherocytosis and increased hypotonic fragility.

The author believes that any child with congenital hemolytic jaundice who is subject to crisis should have a splenectomy performed, preferably between crises. In the presence of a very severe crisis, it is necessary to operate as soon as the patient has been placed in reasonably good condition by carefully spaced transfusions.

GENGENBACH, Denver.

THE DIAGNOSIS AND TREATMENT OF THE PURPURIC DISEASES. ROY R. KRACKE, South. M. J. **34**:56 (Jan.) 1941.

The author stresses the importance of determining the nature of the weakness of the clotting mechanism in all cases of purpura.

The following laboratory studies should be made to determine the exact nature of the defect before any sort of treatment is begun: (1) a complete blood count, (2) a platelet count, (3) a determination of coagulation time, (4) a determination of bleeding time, (5) a tourniquet test, (6) a clot retraction test, (7) a determination of prothrombin clotting time and (8) in some cases a plasma fibrinogen estimation.

The author warns the clinician that when he fails to utilize accepted laboratory procedures in the diagnosis of disease he is on hazardous diagnostic ground and that there are no better examples of this danger than that seen in the purpuric diseases.

SCHLUTZ, Chicago.

THE BLOOD CHOLESTEROL CONTENT IN CHILDHOOD. VIDA J. M. STARK, Arch. Dis. Childhood **15**:255 (Dec.) 1940.

In a group of healthy children the range of blood cholesterol content lay between 96 and 134 mg. per hundred cubic centimeters. In pneumonia, empyema, acute rheumatic arthritis and the early stages of acute nephritis, the blood cholesterol content tended to be low and to rise with convalescence. In children suffering from a second or third attack of pneumonia, the content was low. In nephrosis and obstructive jaundice high blood cholesterol values prevailed, whereas in edema due to other causes and in hemolytic jaundice low values were frequently found.

KELLY, Milwaukee.

ON ACUTE ENDOCARDITIS IN INFANTS. SIEGFRIED WOLFF, Brit. J. Child. Dis. **37**:241 (Oct.-Dec.) 1940.

After reviewing some of the literature on the subject, Wolff gives a report on 2 infants who recovered from acute endocarditis. He emphasizes the fact that the reported cases are practically all based on postmortem reports.

The author quotes H. Finkelstein, who, in 1938, called attention to the triad which he considered of importance in making the diagnosis of acute endocarditis: "an uncommon pallor tending to cyanosis; a striking acceleration and deepening of respiration which cannot be explained by lung disease and which, subjectively, is not apparently felt; finally, repeated attacks of cyanosis in which, as contrasted with asphyxial conditions, there is no stoppage of respiration."

Endocarditis in infants is due chiefly to either influenza or sepsis. Finkelstein found that most of the cases ended fatally after one to four weeks.

The 2 patients with acute endocarditis here reported on were infants about 3 months of age. In both the endocarditis was due to staphylococci. The original foci of infection were boils. One infant acquired a purulent pericarditis, which was aspirated.

LANGMANN, New York.

CONSTITUTIONAL CONGENITAL AFIBRINOGENEMIA AND FIBRINOPENIA IN CHILDHOOD. E. GLANZMANN, H. STEINER and H. KELLER, Schweiz. med. Wchnschr. **70**: 1243 (Dec. 21); 1261 (Dec. 28) 1940.

Glanzmann, Steiner and Keller (Jenner Hospital, Berne) present the comparison between afibrinogenemia and fibrinopenia. In afibrinogenemia there is

almost immediate bleeding after birth (navel hemorrhage), while in fibrinopenia bleeding occurs later, without a history of previous hemorrhage. In afibrinogenemia a persistent lack of fibrinogen is reflected by lack of coagulability of the blood, increased bleeding time and intermittent thrombopenia. In a case of fibrinopenia cited by the authors there was only a passing lack of fibrinogen; the bleeding time was shortened, though an intermittent thrombopenia occurred here also.

The plasma albumin picture is not altered essentially in afibrinogenemia; in fibrinopenia the globulin is increased. The Takata-Ara reaction is negative in the first condition and positive in the second. In afibrinogenemia there are no signs of liver damage; in fibrinopenia, hepatosplenomegaly and icterus are observed. In afibrinogenemia gross hematomas occur characteristically after trauma; in fibrinopenia streaked skin hemorrhages are seen.

ABT, Chicago.

PATHOGENESIS AND TREATMENT OF GENUINE HYPOTENSION. G. SURÁNYI, Orvosi hetil. **84**:267 (May 25) 1940.

Over a period of years 10 children with chronic low blood pressure were observed. Neither a diminution of the epinephrine content of the blood nor hypofunction of the cortical substance of the adrenals could be established as the cause of this condition. The cause of genuine hypotension is probably a "constitutional disorder"; there seems to be no possibility of demonstrating functional disorders of certain endocrine glands.

GÖTTCHE, Budapest.

Diseases of the Nose, Throat and Ear

INDICATIONS FOR DIRECT LARYNGOSCOPY. C. L. JACKSON, Ann. Otol., Rhin. & Laryng. **48**:926 (Dec.) 1939.

In children, obstructive laryngeal dyspnea, stridor, wheezing, hoarseness or aphonia calls for direct laryngoscopic examination. The most common cause of stridor in infancy is congenital deformity of the epiglottis and the subglottic aperture.

A direct laryngoscopic procedure is necessary also for the removal of foreign bodies, for obtaining secretion directly from the larynx or trachea for bacteriologic study and also, in asphyxia neonatorum, for aspiration of laryngeal and tracheal secretions and to exclude a high obstruction.

Adult patients requiring a direct laryngoscopic procedure may be divided into two classes: those in whom the larynx is imperfectly visualized by the mirror and those in whom the view by the mirror is satisfactory but a condition is seen which calls for biopsy, surgical intervention or dilation. Asphyxial death of a drunken, injured or anesthetized patient may sometimes be prevented by lifting the tongue forward by means of the laryngoscope, a catheter or intubation tube being introduced to maintain the airway if necessary.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

DISEASES OF THE SPHENOID SINUS, WITH A REPORT OF A CASE OF A CYST OF THE SPHENOID SINUS. EDWIN B. BILCHICK, Arch. Otolaryng. **32**:1031 (Dec.) 1940.

Because of its position in relation to surrounding areas, diagnosis of disease of the sphenoid sinus is often extremely difficult. Exhaustive study of clinical symptoms is stressed, and the importance of employing every possible procedure and instrument in diagnostic effort is emphasized.

When definite diagnosis is uncertain, exploration of the sinus is advocated, since an untreated condition in this sinus may lead to impairment of vision.

GREENWOOD, Chicago.

ALLERGY OF THE UPPER AND LOWER RESPIRATORY TRACTS IN CHILDREN. FRENCH K. HANSEL, Ann. Otol., Rhin. & Laryng. **49**:578 (Sept.) 1940.

The paper is based on a study of 455 cases encountered in the pediatric allergy clinic of Washington University, St. Louis. This study consisted of a careful analysis of the nasal symptoms of sneezing, itching and obstruction, of gross nasal changes, of the cells of the nasal secretions, of roentgen findings and of bacteriologic findings. It was felt that of all these diagnostic factors the eosinophilia of the nasal and sinal secretions was the most positive sign of allergy. By cytologic study it was also possible to determine the clinical course of the disease in relation to acute, subacute and chronic complicating infection.

Hansel states that, although tonsillectomy is indicated in certain patients who have nasal allergy, it is important to bear in mind that the operation will not materially influence the allergic symptoms except in a small percentage of cases. The indications for tonsillectomy should be the same in children with nasal allergy as in those without nasal allergy, but in any event the operation should be done only after allergic study.

Because edema of the nasal mucosa is commonly associated with nasal allergy, positive roentgen findings are the rule rather than the exception. Roentgenograms should not be taken during a period of acute exacerbation or during an acute or subacute infection, as the findings will then be more pronounced than during the quiescent stage. Hansel feels that the studies indicated that sinus infection is not a common complication of respiratory allergy. He feels, too, that in the reports on sinal disease in children allergy is not given proper consideration as an etiologic factor and that a clear general understanding of sinal disease in children will not come until this is done and until sinal disease is discussed in terms of cytologic findings as well as in terms of other diagnostic procedures.

There is a definite correlation between the cell count of the secretions and the biochemical composition. Watery secretion is usually present when the discharge is profuse, and so the dilution is high and few cells may be seen. Sometimes secretion is scanty, and the flow may be started by the insertion of a tampon saturated with a solution of sodium chloride. Secretion may be obtained from various sinuses by washing. Sometimes centrifugation of the secretions is required. Full directions for making a smear and staining it are presented. Interpretation of the cytologic picture must include consideration of the type and quantity of the secretion and the correlation of this with the history and nasal changes.

There is no definite relationship between blood eosinophilia and clinical symptoms or the number of eosinophils in the nasal secretions.

Nasal allergy may persist without asthma, but often allergic bronchitis appears, which is frequently a forerunner of asthma in children. Asthma may appear in severe form after acute infectious diseases. Whooping cough is the most common cause of its precipitation and measles is the next.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

THE USE OF HUMAN CONVALESCENT SCARLET FEVER SERUM IN STREPTOCOCCIC INFECTIONS INVOLVING THE EAR, NOSE AND THROAT. PIERRE VIOLE, Ann. Otol., Rhin. & Laryng. **49**:639 (Sept.) 1940.

Viole reports the result of using pooled scarlet fever serum in the treatment of hemolytic streptococcus infections. While the use of the serum does not give brilliant results in all cases, there seems to be definite evidence that it is of considerable value. This is particularly true in cases of streptococcic sore throat and cases of laryngotracheobronchitis. If given early enough and in sufficient quantity in the latter, the serum appears to eliminate the need for tracheotomy. Sulfanilamide does not appear to be needed in conjunction with it, but as long as they do not counteract each other, both should be used when indicated. There are no hazards in the use of the serum, and such reactions as occur are easily controlled.

M. V. MILLER, Philadelphia. [ARCH. OTOLARYNG.]

A Survey of the Relation Between Nutrition and the Ear. Grant Selfridge, Ann. Otol., Rhin. & Laryng. **49**:674 (Sept.) 1940.

Selfridge reviews the literature on deficiencies of the various vitamins and the effect of these deficiencies on the function of the eighth nerve and on the incidence and severity of infections. Lack of vitamin A, B or C apparently causes changes in the eighth nerve, in addition to other more general effects. Deficiencies in B and C appear to have a distinct bearing on certain allergic manifestations. All the vitamins are essential during acute infections; they do not shorten the infection, but they seem to aid in sustaining the general physical condition. The tendency to catch cold appears lessened if the diet contains all of the essential vitamin factors in sufficient quantity. M. V. Miller, Philadelphia. [Arch. Otolaryng.]

Treatment of Laryngeal Papilloma in Children. E. N. Broyles, South. M. J. **34**:239 (March) 1941.

The author reports 5 cases of papilloma of the larynx in children. The condition cleared up in about six months when treated with local applications of estrogen. An estimated 1,000 international units (0.1 cc. of amniotin in oil) was applied at each treatment. No secondary sex changes were noted.

Many kinds of treatment have been used for papilloma of the larynx: excision, roentgen or radium irradiation, fulguration, local applications of chemical caustics and subcutaneous injection of testosterone. None of these have been satisfactory.

The author believes that the local application of estrogen has a definite action on the multiple papillomas of children. The characteristics of growth were changed from the infantile to the adult type, which made the treatment simple and far more satisfactory than treatments used in the past. Schlutz, Chicago.

Daily Variations in the Breathing Capacity and Grip Strength of Preschool Children as Related to the Occurrence of Colds. Eleanor Metheny, Child Development **12**:69 (March) 1941.

The relation of day to day variations in the breathing capacity and grip strength to the occurrence of colds was investigated. The subjects, 22 children 4 years old, were tested daily for two periods, of four weeks and six weeks respectively. Decreases in grip strength and in breathing capacity were found to occur more frequently on the days prior to the occurrence of a cold than on days not followed by a cold. Criteria were set up for the "prediction" of colds one or two days previous to the actual occurrence of the cold. Tetrachoric correlations between predictions of "cold" or "no cold" and the occurrence or non-occurrence of a cold ranged from 0.54 to 0.81, the actual figure depending on the criterion used. Author's Summary.

The Psychology of Deafness in Children. George L. Drennan, Illinois M. J. **79**:227 (March) 1941.

Defective hearing imposes mental strain, isolation and loneliness on the deaf and hard-of-hearing child and arrests his intellectual development. His continual struggle to make himself understood may result in a marked inferiority complex. Many of the psychologic reactions to deafness may be helped. The prevention of those diseases which produce deafness is most important.

Barbour, Peoria, Ill.

Cold Vaccines: A Further Evaluation. H. S. Diehl, A. B. Baker and D. W. Cowan, J. A. M. A. **115**:593 (Aug. 24) 1940.

In 2 controlled studies the authors used first a vaccine in which the organisms had been destroyed by mechanical means and then one in which they were destroyed by heat. In both studies the reduction in the number of colds was

about the same in students treated with the vaccine as in students used as controls, who were treated merely with salt solution. The vaccine, however, produced some rather severe reactions.

HEERSMA, Kalamazoo, Mich.

THE INCIDENCE OF HAEMOLYTIC STREPTOCOCCI IN THE THROATS OF OBSTETRIC NURSES: RESULTS OF TREATMENT BY TONSILLECTOMY AND SULFANILAMIDE. J. N. CHESTERMAN and S. SCANDRETT, M. J. Australia **2**:695 (Dec. 28) 1940.

The authors' study shows that nurses working in an obstetric hospital to which is attached an isolation block for the treatment of puerperal infections run considerable risk of acquiring hemolytic streptococci in the upper respiratory tract. This risk is greatly increased by the presence of tonsillar tissue. Tonsillectomy proved successful in eliminating the infection from the throat in the majority of instances. When tonsillectomy alone was not enough, sulfanilamide overcame the infection. However, sulfanilamide was not effective in the presence of pronounced abnormality of the upper respiratory tract.

GONCE, Madison, Wis.

SEVERE MASTOIDITIS. A. SARGNON, Oto-rhino-laryng. internat. **24**:225 (Aug.) 1940.

During the winter of 1939-1940 Sargnon observed 3 cases of severe mastoid infection. In 1 case the infection was complicated by superacute osteomyelitis, with spontaneous hemorrhage into the mastoid cavity. The second case was that of a child with an infection due to Löffler's bacillus and phlebitis of the lateral sinus. The third was that of a child in whom facial paralysis occurred forty-six hours after the onset of otitis. This patient was operated on immediately and made an unusually quick recovery. The other 2 patients also recovered.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

HISTOLOGIC OBSERVATIONS ON THE BLOOD VESSELS AND THE LYMPHATIC NODULES AND ON THE EVENTUAL INCLUSION OF CARTILAGE AND BONE IN THE FAUCIAL TONSIL. G. ZANZUCCHI, Arch. ital. di otol. **52**:443 (Sept.) 1940.

The material for this study consisted of the tonsils removed at autopsy from 30 subjects who had presented no evidence of pathologic alterations of the tonsils. The subjects varied in age from 7 months of fetal life to 79 years. Attention was directed to the structure of the blood vessels, the fatty infiltration of the reticular cells of the lymph nodules and the inclusion of cartilaginous and osseous tissue in the tonsil.

For the study of the structure of the blood vessels, the material was divided into two groups: (*a*) arteries in the presumably normal tonsils and (*b*) arteries in the tonsils in involution. It is characteristic that in tonsils in which the lymphatic tissue does not present signs of regression the small arteries preserve their juvenile character to advanced age. In tonsils of this kind, elastic fibers in the vessel walls were scarce or entirely lacking. On the other hand, in those in which the lymphatic tissue was in regression and gave place to fibrous tissue, elastic fibers, even in the small arteries, were very abundant in the intima, in the media and between the latter and the adventitia and soon showed a tendency to liquefaction. Thickening of the walls of the vessels and partial obliteration of the lumens proceed pari passu. Soon areas of fatty infiltration appear here and there. Therefore, it may be concluded that senile characteristics in the parenchymal arteries are manifested only in the areas of regression of the lymphatic tissue, never where the latter is conserved.

A characteristic finding, observed in all the subjects, independent of age, was the considerable lipid content of the reticular cells in the clear centers of the lymph nodules. The probable explanation of this phenomenon is the assumption by these cells of fatty material diffused in the interstitial lymph, derived from the mass of fatty material contained in the tonsillar crypts. The fatty granules observed in the large globular cells of the clear centers probably represent fat derived from the degeneration of lymphocytes and phagocytosed by these cells.

The inclusion of cartilaginous and osseous tissue in the capsule and septums was observed in tonsils from subjects from 8 to 70 years of age. While primary ossification may occur, by far the most frequent process is chondrification, which may be followed by ossification. Zanzucchi discusses at length two theories of the source of the bone and cartilage: whether it is (*a*) an embryonic rest in the second branchial arch or (*b*) aberrant germs in the branchial skeleton. His conclusion, supported by a study of serial sections of the tonsils of 24 human fetuses, is that in all cases chondrification or the presence of osseous spicules depends on strictly local circulatory conditions. The claim that the cartilaginous nodules are supplied with perichondrium in children and not in the aged is not borne out by his observations. Osseous inclusions are sometimes independent from cartilaginous inclusions and are undoubtedly the result of membranous ossification. Many other times ossification occurs through metaplasia of the cartilaginous tissue or, more frequently, by substitution of bony tissue for the cartilage. The substitution proceeds directly inward from the perichondrium and not from the center toward the periphery.

DENNIS, San Diego, Calif. [ARCH. OTOLARYNG.]

ROENTGEN TREATMENT OF CHRONIC TONSILLITIS. VOGEL, Ztschr. f. Hals-, Nasen- u. Ohrenh. **46**:195, 1939.

Vogel reports a series of cases in which chronic tonsillitis was treated with high voltage roentgen radiation. Since the results were so varied and inconclusive, he believes that surgical removal of the tonsils should remain the procedure of choice, as this operation is usually safe and the results are rarely in doubt.

Roentgen therapy produces rather uncertain results. There is no indication that the tonsils can be completely resorbed or will become fibrotic or that the infection within the tonsils can be completely destroyed. Furthermore, the treatment is always prolonged, requiring about three months for a complete course.

However, the author believes that this method of treatment is indicated for certain types of patients. These are the senile, the arteriosclerotic, those with cardiac insufficiency and those with hemophilia and other allied conditions.

PERSKY, Philadelphia. [ARCH. OTOLARYNG.]

Nervous Diseases

DERMATOLOGIC ASPECTS OF TUBEROUS SCLEROSIS. THOMAS BUTTERWORTH and MCCLELLAN WILSON JR., Arch. Dermat. & Syph. **43**:1 (Jan.) 1941.

Tuberous sclerosis refers to the potato-like nodules occurring in the cortex of the cerebral hemispheres, a phenomenon associated with varied changes in the skin. The most characteristic of these changes is adenoma sebaceum, which occurs as a papular and nodular eruption of the face. The condition is frequently associated with mental deficiency and epilepsy. These conditions constitute a triad known as epiloia.

Tuberous sclerosis occurs in all races. It is more common in Europe than in the United States. Most of the cases in this country have been reported from institutions for patients with mental disease.

The disease occurs in early life and affects the two sexes equally. Hereditary and familial features are prominent, and it is probably transmitted as an incompletely dominant trait.

Any phase of the triad of adenoma sebaceum, epilepsy and mental deficiency may be poorly developed. One of the triad of symptoms may exist alone, or any two may occur in the absence of the third.

The mental and neurologic symptoms of tuberous sclerosis are given. A classification of the cutaneous changes occurring in the disease is offered, with a detailed description of each manifestation.

JACKSON, Iowa City.

PNEUMOCOCCIC MENINGITIS: A REVIEW OF ENGLISH LITERATURE WITH A REPORT OF TWO CASES IN WHICH THE DISEASE WAS OF OTITIC ORIGIN. GOODLATTE B. GILMORE and PHILIP SACKS, Arch. Otolaryng. **32**:1007 (Dec.) 1940.

The authors present 2 cases of pneumococcic meningitis and outline a course of therapy inducing eventual recovery. The importance of dividing meningitis into protective and suppurative types in relation to prognosis and therapy is stressed. Demonstration of the organism in a spinal fluid culture should be the only basis for diagnosis of a bacterial meningitis. The use of autogenous vaccine made from a culture of material from the mastoid during operative intervention was shown to be of value in minimizing the danger of meningitis as a complication of acute mastoiditis due to the type III pneumococcus.

The use of specific serum and sulfapyridine in a certain phase in the treatment of pneumococcic meningitis is discussed. It is pointed out that the former helps the body forces involved in destroying organisms and neutralizing evolved toxins, and that the latter inhibits the organism but does not destroy it.

The timeliness of surgical drainage and operation is discussed.

GREENWOOD, Chicago.

A METHOD OF DIAGNOSING IDIOPATHIC EPILEPSY. F. C. DE LORENZO, J. Pediat. **17**:355 (Sept.) 1940.

The antidiuretic and superhydration test introduced by McQuarrie for the diagnosis of epilepsy was performed on 17 patients with convulsions. In 10 of the patients idiopathic epilepsy had been diagnosed; 9 of these 10 reacted positively to the McQuarrie test. The other 8 reacted negatively to the test, as did 17 normal children used as controls. The method of procedure of this test is outlined in detail.

RAUH, Cincinnati.

PROGNOSIS IN POSTENCEPHALITIC BEHAVIOR DISORDERS. PHILIP H. HEERSEMA, M. Clin. North America **24**:1179 (July) 1940.

When unaccompanied by obvious neurologic stigmas, such as unequal reflexes, ocular paresis or tics, postencephalitic behavior disorders may present an exceedingly difficult problem in diagnosis. If there is a history of previous virus diseases, especially if such diseases were accompanied by symptoms such as hypersomnolence or reversal of sleep routine, diplopia, or ocular palsies and a mild state of confusion, the relationship of the behavior disorder to the virus disease should be seriously considered. Typically such behavior disorders are characterized by impulsive, aggressive conduct, ranging from the mischievous to the criminal. This aggressiveness or compulsion is the feature which dominates the child's conduct. Emotionally the child is unstable and volatile, irritable, cruel or mawkishly affectionate.

These disorders occur almost exclusively in children and in adolescents. In adults there is little danger of intellectual deterioration as a result of encephalitis. The greatest danger of subsequent mental deficiency is encountered when the disease occurs before the patient reaches the age of 5 years. At this early age, a disease which may not be severe enough to cause motor damage may yet so interfere with those organizing processes proceeding in the brain, and having to do with assimilation of sensation, perception of new concepts and moral values, as seriously to interfere with the organization of the child into a normally functioning unit. It is these behavior elements which are most severely affected in typical postencephalitic disorders. In Heersema's opinion the damage preceding the behavior disorder occurs largely in the frontal lobe and is diffuse and relatively mild. In children who have so far recovered that all neurologic symptoms have disappeared and only the behavior disorder remains, it may be assumed that the disease has temporarily or permanently disorganized (retarded) the developmental process rather than produced objective histopathologic evidence of destruction.

The prognosis of encephalitic sequelae is poor. Up to the present, attempts at prophylaxis during the acute illness and convalescence have been disappointing. The same is largely true of efforts at rehabilitation. Of measures designed to prevent sequelae, rest is probably the most important.

EUGENE SMITH, Ogden, Utah.

FAVORABLE TYPES OF BRAIN TUMOR AND THE RESULTS OF THEIR OPERATIVE REMOVAL. GILBERT HORRAX, New England J. Med. **224**:307 (Feb. 20) 1941.

This study is based on the hospital records and follow-up reports (by personal interview or letter) of 400 consecutive patients with tumors of the brain that were verified pathologically from November 1932 to June 1939. Of this total number, the author has classed 224, or 56 per cent, as favorable tumors. By the term "favorable" as here used is meant tumors that were capable of complete and permanent removal, resulting in cure of the patients. Of the 224 favorable tumors, 80 were meningiomas, 33 acoustic neuromas, 30 pituitary adenomas, 29 gliomas (mostly cystic) and 52 miscellaneous tumors, such as angiomas, hemangiomatous cysts and pinealomas.

Among the 224 patients with favorable tumors there were 27 operative deaths, a mortality of 12 per cent. This leaves 197 survivors; but of these, 10 have died subsequently, leaving a final figure of 187 patients who are living and whose tumors the author believes to have been wholly eradicated. Of these, 27 have severe disabilities that prevent them from living useful lives. This leaves a final total of 160, or 71 per cent of the original 224, who not only have survived but are leading useful lives with little or no functional loss.

GENGENBACH, Denver.

SPECIFIC POLYSACCHARIDE AS CUTANEOUS TEST FOR EVALUATION OF SERUM THERAPY IN INFLUENZA BACILLUS MENINGITIS. JOHN H. DINGLE and LEAH R. SEIDMAN, Proc. Soc. Exper. Biol. & Med. **46**:34 (Jan.) 1941.

Intracutaneous injections of 0.01 mg. of polysaccharide isolated from Haemophilus influenzae type B in 0.1 cc. of physiologic solution of sodium chloride (1:10,000 dilution) were made in 7 patients with influenza bacillus meningitis treated with anti-influenza-bacillus horse serum. In no instance did an immediate (twenty minute) or delayed (twenty-four hour) reaction indicate the presence of the demonstrable excess of antibody. On the other hand, rabbit antiserum produced an immediate wheal in five instances two to eight hours after the administration of serum. Normal persons were shown to have an immediate response to rabbit antiserum but not to horse antiserum. Further work may establish this technic as a useful guide to the adequacy of serum therapy for influenza bacillus meningitis.

HANSEN, Minneapolis.

CEREBELLAR SUBDURAL HEMATOMA IN INFANT TWO WEEKS OLD WITH SECONDARY HYDROCEPHALUS. R. G. COBLENTZ, Surgery **8**:771 (Nov.) 1940.

Coblentz presents the history of an infant 2 weeks of age who recovered after an operation for an encysted subdural hematoma. The author believes that his is the first case in which such a lesion has been recognized during life and cured by operation. The hematoma was located over the right cerebellar hemisphere. Secondary hydrocephalus also was present. Although there was no definite history of trauma, ecchymosis of the upper lids and a moderate occipital caput led the author to suspect a slight trauma as the most likely etiologic factor. Continued increased intracranial pressure and prompt disappearance of blood in the lumbar subarachnoid fluid after daily lumbar punctures indicated a coexisting lesion. Subdural hematoma over the cerebral hemispheres was ruled out by subdural taps. Ventriculographic examination definitely located the lesion in the posterior fossa.

Evacuation of the clot through a small trephine opening without drainage effected a cure. At the time of writing, the baby was 3 months old and had made a complete recovery. J. A. M. A.

PRIMARY INFECTIVE POLYNEURITIS. B. F. SAMPSON, South African M. J. **15**:23 (Jan. 25) 1941.

Sampson emphasizes the need of thoroughly considering the possibility of cresylic compounds, especially triorthocresol phosphate, as the cause of an epidemic of peripheral multiple neuritis which has the characteristics of supposed infective polyneuritis of virus origin. GONCE, Madison.

Skin Diseases; Allergy

ULCERATIVE REACTION FROM GENTIAN VIOLET IN THE TREATMENT OF IMPETIGO CONTAGIOSA. LEON GOLDMAN, Arch. Dermat. & Syph. **42**:1122 (Dec.) 1940.

Ulceration has been seen in 4 cases of impetigo contagiosa; 2 of the patients were infants and 2 were adults. In these cases, a smooth gentian violet crust formed over the impetigo areas. Instead of curling up, shrinking and peeling off, as the usual gentian violet crust does, the crusts in these instances remained fixed firmly to the skin for a relatively long period, in all cases more than two weeks and in 1 case five weeks. The skin adjacent to the adherent crust showed no redness, tenderness or edema. However, when the crust was removed either with wet dressings or with scissors and forceps, a deeply punched-out area filled with pus was found. With irrigation and application of mercury ointments these areas healed rather rapidly but left ugly punched-out scars, some resembling a postvaricella scar and others the depressed scar of an ecthymatous ulcer. These were seen chiefly on the face; in 1 infant they were also found deep in the axilla. There was no evidence of hypersensitivity to gentian violet in any of the cases.

This complication of the gentian violet treatment of impetigo contagiosa must be uncommon when one considers the popularity of the method. The complication should be suspected when there is no evidence of separation of a gentian violet crust after an arbitrary period of approximately two weeks. The clinical survey does not suggest any reason why this reaction has occurred with gentian violet and not with the other occlusive or crusting methods. Perhaps if the other methods had been used as frequently as the gentian violet treatment, this unusual complication would have been encountered in cases in which those methods were used. JACKSON, Iowa City.

LICHEN STRIATUS. FRANCIS EUGENE SENEAR and MARCUS RAYNER, Arch. Dermat. & Syph. **43**:116 (Jan.) 1941.

The authors describe 10 cases in each of which there was a linear lichenoid papular eruption. With but a single exception this eruption involved the upper extremity and was unilateral. In 7 of the 10 cases the patient was a child.

In all cases the onset was sudden and the extension of the eruption to form linear bands was rapid. The eruption was of short duration and was self limited. As a rule, the disease was asymptomatic.

The eruption was composed of primary and lichenoid papules which often coalesced to form patches of lichenified dermatitis. The clinical appearance and the history usually permitted ready differentiation of the disease from naevus unius lateris, lichen planus and psoriasis.

The histologic study of sections of tissue taken from 2 of the patients showed the changes of lichenified dermatitis.

The authors believe that the existence of a clinical type of linear eruption with the characteristics they have outlined should be recognized. Lichen striatus is suggested as a suitable name for this disease. JACKSON, Iowa City.

ECZEMA IN INFANTS AND YOUNG CHILDREN. LEWIS WEBB HILL, New England J. Med. **223**:624 (Oct. 17) 1940.

Eczema in infants and young children may be caused by allergy to foods, to inhalants, to organic or inorganic contactants, by fungous or low grade pyogenic infection or by chemical or mechanical irritation. However, in most cases it is due to allergy.

Typical allergic eczema, or "atopic dermatitis," seldom begins before the age of 3 months. The diagnosis of atopic dermatitis in an infant is suggested by the character of the eruption and the severe itching, and may often be confirmed by positive results of cutaneous tests. A positive reaction to a scratch test is usually of etiologic significance; a positive reaction to an intracutaneous test may or may not be.

A combination of immunologic and local treatment is much better than either alone. Many infants are relieved of their dermatitis when certain foods, notably milk and wheat, are removed from the diet.

In dealing with sensitivity to milk in eczema, goat's milk or a milk-free food may be of value. Milk-free foods, most of which are made of soybean flour, sometimes cause bulky, loose bowel movements and irritation of the buttocks. If the formula is cooked in a double boiler for three quarters of an hour, this tendency is considerably lessened.

Wheat is the most allergenic of the cereals. Oranges, too, frequently cause reactions; even when cutaneous reactions to orange are negative, it is not uncommon for itching to be severer after taking it. Of the vegetables, peas and spinach are the most allergenic. Sensitivity to feathers is not uncommon, and silk and kapok are occasionally causes of dermatitis.

Face masks are not recommended. A rectangle of cellophane taped to the part of the bed sheet underneath the head is valuable in preventing trauma due to rubbing. Neither lotions containing insoluble powders nor salves are desirable, as a rule, during the acute, weeping stage. Wet compresses of 2 per cent resorcinol or tannic acid solution containing 2 per cent boric acid, 1 per cent aluminum acetate solution or 0.05 per cent potassium permanganate solutions are better. Some of the white tar preparations on the market are fairly satisfactory, but none are so good as coal tar ointment. The latter should not be employed, however, if pyogenic infection is present.

House dust causes dermatitis more often by inhalation than by outside contact.

GENGENBACH, Denver.

THE PATHOLOGIC PHYSIOLOGY OF BRONCHIAL ASTHMA IN CHILDREN (WITH REFERENCE TO THE ROLE OF INFECTION). HENRY N. PRATT, New England J. Med. **223**:626 (Oct. 17) 1940.

The fundamental pathologic physiology of all atopic and anaphylactic phenomena is increased capillary permeability, smooth muscle spasm and excessive mucus secretion.

The part played by infection may be divided into four categories: bacterial allergy; infection of the respiratory tract acting as a trigger mechanism; infection secondary to the asthmatic attack, and focal infection. It has often been predicated that a child may become sensitized to bacteria which he harbors somewhere in the respiratory tract. The occasional satisfactory result following therapy with autogenous or stock vaccine is in most cases due to shock and is entirely nonspecific.

Infection of the respiratory tract, such as the common cold, often precipitates an asthmatic attack in an atopic child. The child is usually sensitive to some food or inhalant which he can tolerate except in the presence of infection. This has been clearly demonstrated over and over again by abolishing the extrinsic factor; the child then has a cold without asthma.

Infection may be secondary to an attack of asthma initiated by some extrinsic factor to which the child is sensitive. Such an infection probably originates in

the inadequately aerated parts of the lungs. Once established, it may produce a chronic irritation in the bronchi which causes the attacks of asthma to continue intermittently for several weeks.

Focal infection seldom plays a part in childhood asthma. In an allergic child the lymphoid structures in the upper respiratory tract tend to hypertrophy, so that one is sorely tempted to remove the large, boggy tonsils and adenoids. Statistically it has been shown that removal of these structures has no lasting effect on the asthma.

GENGENBACH, Denver.

THE TREATMENT OF BRONCHIAL ASTHMA IN CHILDREN. ETHAN ALLAN BROWN, New England J. Med. **223**:629 (Oct. 17) 1940.

Acute attacks of bronchial asthma in children can be treated by any of the sympatheticomimetic drugs of the ephedrine group. Ephedrine sulfate is the best; the usual dose is ⅜ grain (0.024 Gm.). However, it has undesirable side actions, and it is necessary that additional sedatives be given. The best of these is undoubtedly phenobarbital, since many of the barbiturates are vasospasmodic. It may be given in doses of ¼ or ½ grain (0.016 or 0.032 Gm.). For acute attacks of greater severity, small doses of epinephrine hydrochloride solution (1:1,000), 2 or 3 minims (0.012 or 0.018 cc.), may be injected subcutaneously. The dose may be repeated every fifteen minutes for four doses, if necessary. In cases in which ephedrine sulfate given by mouth is not necessarily effective by itself, it will enhance and prolong the action of the epinephrine. Rectal medication seems effective in children who cannot take the drug orally.

In the severer attacks, epinephrine base in oil, 0.5 to 0.8 cc. of the usual (N. N. R.) preparation (2 mg. per cubic centimeter), should be given every twelve hours, with ephedrine sulfate given by mouth at the time of injection and six hours later. Status asthmaticus is not common in children, but when it does occur it requires the treatment given to adults. Theophylline with ethylenediamine, administered intravenously, is used, the dose being 3½ grains (0.225 Gm.); 50 cc. of a 50 per cent solution of sucrose is given at the same time. Epinephrine hydrochloride solution, 1:1,000, may also be given intravenously with this injection, the dose being 0.1 or 0.2 cc. Ether in olive oil (30 cc. of ether to 60 cc. of oil) given rectally will also help to break a severe asthmatic attack. Morphine in any dose and in any form has a deadly effect on an asthmatic child; it should never be used under any circumstances whatsoever. Epinephrine given by inhalation has been utilized, but it is very difficult to teach a child inhalation therapy.

For children with the extrinsic type of asthma, a change in environment is imperative. For those with the intrinsic type, any intercurrent infection can be cared for more easily in the hospital than at home. For those with continuous, chronic asthma, any one of the several remedies containing potassium iodide and tincture of stramonium may be employed. The general care of the child still remains the most vital factor.

GENGENBACH, Denver.

Miscellaneous

THE ACTIONS OF METHYL-ATROPINE NITRATE (EUMYDRIN). J. D. P. GRAHAM and S. LAZARUS, J. Pharmacol. & Exper. Therap. **70**:165 (Oct.) 1940.

In the past three or four years favorable results have been reported from the use of this drug in the treatment of pyloric stenosis in infants; to one who is not impressed with the efficacy of atropine in the therapy of this condition the published results did not seem very impressive. The authors found that atropine methylnitrate had relatively the same action on segments of rabbit intestine and on the intestine of anesthetized rabbits as did atropine sulfate. The spasmolytic action against neurogenic spasms induced by physostigmine salicylate was the same as that of atropine sulfate. The toxicity of the drug for mice was about one-third that of atropine sulfate. From this work one would not expect any better results from the use of atropine methylnitrate than from the administration of atropine sulfate in the treatment of pyloric spasm in infants.

PILCHER, Cleveland.

CARE OF CHILDREN IN WAR-TIME AND AFTER. LEWIS THATCHER, Edinburgh M. J. **47**:836 (Dec.) 1940.

The author discusses the improvements which have occurred steadily in the care of children in Scotland and also the menace to life still resulting from birth accidents and prematurity. Dietaries still need to be improved, in regard to both quality and quantity. The vitamin content of the present day highly milled flour and cereals is small, and the quantity of food is not sufficient.

During the first World War the trustees of the Carnegie fund attempted to make provisions for promoting the physical welfare of children and mothers. At the beginning of the present war, many children were evacuated and dispersed from their homes, under the workings of a marvelous organization. Some town children had to be returned home, but generally the newcomers were adjusted to the new family life and have received great benefits therefrom. More has resulted than the attainment of safety, for it has shown to all citizens that slums still exist and that dirt and destitution have been a part of the environment of many children. Knowledge of the poor physical development, uncleanliness and ignorance of ordinary social conduct shown by many such children has now been disseminated throughout England.

Realizing the mistakes of the past, Thatcher urges a forward look toward the clearance of slums; there must be assurance of adequate housing and home equipment and the provision of an environment that will conduce to good work, health, happiness and the rearing of normal children. New communities are arising and being so equipped that they provide better for childbearing, child welfare and school and urban life. The family physician, rather than the physician in an impersonal bureaucratic service, should be an indispensable personal factor in the home life.

NEFF, Kansas City, Mo.

SULFAPYRIDINE TREATMENT IN CHILDREN. M. COTELLESSA, Riv. di clin. pediat. **38**:669 (Nov.) 1940.

Sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) was given to 50 infants under 12 months of age suffering from infections of the respiratory tract, including rhinopharyngitis, tracheitis, bronchitis, pneumonia, bronchopneumonia and bronchopneumonia complicated by whooping cough. The drug was highly efficacious, the temperature having become normal within twenty to thirty hours, and often sooner. The improvement was slower in the cases in which the condition was complicated by whooping cough. Vitamin C is indicated as a supplement to the sulfapyridine therapy.

HIGGINS, Boston.

NEW METHOD OF TAKING NURSLINGS' TEMPERATURES. GUSTAV PAPP, Wien. klin. Wchnschr. **54**:93 (Jan. 31) 1941.

Papp believes that temperature testing at the infant's neck is more hygienic than rectal testing and just as accurate. He has invented a thermometer only 7.5 cm. in length, which he calls a "cerilla" (coined from the words cervix and axilla, since it may be used to take temperatures at either point). The reading is taken at the neck by placing the thermometer under the chin, with the head bent forward, or in the folds of the neck, with the head rotated to the side and tilted so that the lobe of the ear rests on the shoulder; in either position the head may be given support by a small cushion, or even a folded flannel diaper, placed under the head. About ten minutes is required for the thermometer to register accurately at the neck, though five minutes may suffice if the infant is already asleep in the proper position. If the child is restless, measurement in the axilla may be more practical, parallel to body length, and the arm should be fixed to the trunk with an elastic band. This thermometer is also suitable for use in the mouth of a premature infant, but not of a full term baby, since the latter has the strength to bite and break it.

ABT, Chicago.

Book Reviews

The Modern Treatment of Syphilis. By Joseph Earle Moore, with the collaboration of Jarold E. Kemp, Harry Eagle, Paul Padget and Mary Stewart Goodwin. Price, $7.00. Pp. 674, with 98 illustrations and 120 tables. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

The second edition of this excellent book presents the end results of a study of 35,000 cases of syphilis at the Johns Hopkins Hospital. The work represents not only the study of the collaborators of this book but the research of many predecessors at the same hospital.

It is written from the standpoint of both the syphilologist and the internist and for that reason must appeal to all students of medicine.

Certainly no specialty can claim the full responsibility for the treatment of syphilis, and the author stresses the fact that syphilis is not a disease that can be treated at different stages by the dermatologist, the urologist, the syphilologist or the neurologist. The scope of the treatment is so wide that on many occasions one requires a consultant experienced in the treatment of syphilis in order to choose a therapeutic procedure which can benefit the patient.

The manuscript is written in simple vein. The information is easily gotten, and problems studied in different cases are so well presented that one may be sure to find the solution in some chapter of this volume. Certainly one who has a wide acquaintance with medicine in general will feel safer in treating his patients with this book in his office.

There seems to be unlimited information gathered by Moore and his collaborators, not only from their own clinics but from the work of other physicians interested in syphilis. Since the first edition appeared there has been much new information gathered on antisyphilitic treatment. This is especially true with administration of mapharsen, oral use of bismuth preparations, continuous intensive treatment of early syphilis and further developments in the treatment of neurosyphilis and latent syphilis.

The pediatrician will be especially interested in the chapter on congenital syphilis. It is well written and well coordinated with the rest of the volume.

The boxed outlines in each chapter give one a minute review of the treatment as outlined at length and refreshes one's memory at a glance.

The chapter on public health aspects adds much to the interest of the reader, and the bibliography has been outlined sufficiently for one to be able to follow in detail the articles as outlined in the book.

Elimination Diets and the Patient's Allergies: A Handbook of Allergy. By Albert H. Rowe, M.D. Price, $3.00. Pp. 264. Philadelphia: Lea & Febiger, 1941.

For the uninitiated pediatrician this small volume may be found useful as an introduction to general allergy, for it contains much useful information on the subject as a whole.

The title is, however, misleading, for the elimination diets comprise only about 50 pages, with a great deal of unnecessary repetition.

When Rowe came out with his elimination diets in 1926, it was thought by many that the food problem could thus be handled intelligently. However, the method is peculiarly clumsy and so empiric that from a practical standpoint it has been abandoned by most allergists. The subject has been further complicated by the observation that even in early childhood allergic persons are found sensitive to environmental substances as well as to foods. Therefore, if a particular food is

eliminated and the child still has allergy, it is difficult to know which is the incriminating substance—the food or the environmental allergen.

The experience of Rowe is chiefly with adults, and there is no doubt that elimination of many foods may well relieve symptoms, but the pediatrician will find little help in applying the suggested diets to young children. For example, diet 4 suggests the use of 2 or 3 quarts (1.9 to 2.8 liters) of milk daily, and other diets introduce foods which may conceivably upset a child's digestion or actually be an inciter of a new sensitivity.

Rowe particularly frowns on the use of heat-denatured foods, which in the hands of most pediatricians has proved successful. Such denatured foods as evaporated milk, hard-boiled eggs, pablum and other precooked cereals are being used in ever increasing frequency and are daily proving their value.

This small book is nevertheless provocative and should stimulate the pediatrician to a greater interest in the problems of allergy which confront him.

The Avitaminoses: The Chemical, Clinical and Pathological Aspects of the Vitamin Deficiency Diseases. Second edition. By Walter H. Eddy, Ph.D., and Gilbert Dalldorf, M.D. Price, $4.50. Pp. 519, with 69 illustrations and 43 tables. Baltimore: Williams & Wilkins Company, 1941.

One cannot but admire the courage and energy which were essential to undertaking and completing such a comprehensive treatise on a subject that is advancing so rapidly. The nutritionist will here find a background of the chemistry and clinical aspects of the vitamins that will be most helpful. The biologic chemist should obtain much from the clinical portions of the book, and the clinician will benefit greatly by reading the chemical portions.

It is inevitable that the rapidly increasing knowledge in the fields of biologic chemistry, nutrition and clinical medicine renders a book of this type old in many respects even at the time of its publication. The quantitative designation of thiamine, riboflavin and ascorbic acid in terms of international units reflects a usage that is now outmoded by the ability to designate these substances in terms of milligrams. The designation throughout much of the book of the various B factors by an alphabetic letter does not reflect the best modern nomenclature.

Since the publication of the book less than a year ago, rapid advances have been made in knowledge of the effect of riboflavin deficiency in human subjects. Similarly the section on the methods of studying avitaminoses already needs considerable augmentation to bring it up to date, since many new laboratory procedures for the diagnosis of early vitamin A, thiamine, riboflavin, nicotinic acid and ascorbic acid deficiencies have been proved to be of clinical value within the past year.

These are limitations which are inherent in the subject and could not have been avoided by the authors. It is evident from the book that they have given much time and thought to its preparation, and they should be congratulated on the manner in which they have dealt with this very difficult assignment.

Nutritional Deficiencies. By John B. Youmans, M.D., assisted by E. White Patton, M.D. Price, $5. Pp. 385, with 16 illustrations. Philadelphia: J. B. Lippincott Company, 1941.

Each vitamin is taken up from the standpoints of history, nature and function, pathology, incidence, symptoms, diagnosis and treatment. Those discussed are vitamin A, thiamine, nicotinic acid, riboflavin and vitamins C, D, E and K. Protein deficiency, iron deficiency, iodine deficiency and other possible nutritional deficiencies are also included. The second section of the book is devoted to principal dietary sources of essential food factors and laboratory methods for the diagnosis of deficiency diseases.

This book is very well written and almost impossible to put down when once commenced, which I believe sets a new high record for any book on diet. The immense amount of work done on deficiency diseases and vitamins in the past few years has been carefully sifted, and only that essential and of value has been

utilized. The authors' viewpoint is sane and well balanced. For example, the statement "Vitamin-E deficiency, like a deficiency of vitamin K, is a deficiency disease in which there is little need or place for general preventive or prophylactic treatment, the use of the vitamin being confined almost entirely to the relief of specific individual cases under strict medical direction" makes the reviewer wish to applaud.

Most books of this nature are loaded down with useless references. Here references are few and well chosen and placed at the end of each chapter. The photographs are excellent, and the volume is well edited and printed. Altogether this makes a most excellent book for the physician in any field of medicine, and one that he can refer to the omnivorous layman without fear of his obtaining any peculiar or erroneous ideas.

Blood Disorders in Children. By I. Newton Kugelmass, M.D., Ph.D., Sc.D. Spec. Price, $10.00. Pp. 897, with 152 illustrations. New York: Oxford University Press, 1941.

The arrangement of this book differs somewhat from that usually given in works on hematology in that the author has attempted to set up a broad view of the disorders of the blood from a clinical rather than a hematologic viewpoint. It is divided into six sections. The first deals with the hemopoietic system, discussing the formation of the blood and blood-forming organs. The second considers diseases of the erythron, which includes the anemias, polycythemias and pigment disorders. The third part takes up disorders of the white cells, the leukon. These include the myeloid, lymphoid and monocytic disorders and the leukemias. The fourth part, on diseases of the thrombon, deals with the essential and vascular hemorrhagic disturbances. The last two sections are devoted to diseases of the reticuloendothelium and diseases of the organism, which include systemic disorders and infectious diseases. The appendix contains a clever scheme for symptom diagnosis and blood diagnosis arranged alphabetically.

As may be seen, this is a rather ambitious undertaking, and on the whole it is rather well done. It is well written, well organized and up to date. All of the later theories on the blood dyscrasias are discussed and evaluated, and the various treatments are thoroughly discussed. This of course is of great value to one practicing clinical pediatrics. There are also many tables and outlines of symptoms, diagnosis and treatment which are cleverly constructed to stick in the mind of the reader and should be of considerable benefit to students.

Synopsis of the Preparation and Aftercare of Surgical Patients. By Hugh C. Ilgenfritz, M.D., and Rawley M. Penick Jr., M.D. Price, $5.00. Pp. 532, with 55 illustrations and 3 tables. St. Louis: C. V. Mosby Company, 1941.

This 500 page book covers most of the problems having to do with the care of surgical patients, omitting the technic of the actual surgical operation. The technic of routine laboratory procedures is also omitted.

Members of busy clinics, interns in well organized surgical services and surgeons who regularly read three or four of the national surgical journals will not need this book, but it will fill a real need for an occasional surgeon. The book is well written and it gives a well balanced account of the general problems in this field.

Vitamia K en pediatria. By Juan P. Garrahan, Gualterio F. Thomas and Alfredo Larguía. Pp. 102, with 16 illustrations. Buenos Aires, Argentina: El Ateneo, 1942.

The authors present a recapitulation of the chemistry and physiology of vitamin K in particular relation to hemorrhagic disease of the newborn. In their own studies they found that 47, or 11.9 per cent, of 395 newborn infants had pathologic hypothrombinemia; 20, or 42.55 per cent, of these had hemorrhagic disturbances. The Kato method of prothrombin estimation was used in the studies that gave these rather remarkable results.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
General Secretary: Dr. Kenneth D. Blackfan, 300 Longwood Ave., Boston.
Assistant Secretary-Treasurer: Dr. Charles F. McKhann, University of Michigan, Ann Arbor, Mich.

Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Pediatric Association

President: Prof. Charles McNeil, 44 Heriot Row, Edinburgh, Scotland.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht, Holland.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340, 's Gravenhage, Holland.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

SOCIEDAD CUBANA DE PEDIATRÍA

President: Dr. Clemente Inclan Costa, Marique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Velado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Ernesto Vizcarrondo, Venezuela.
Secretary: Dr. E. Santos Mendoza, Venezuela.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Conrado Pelfort, Av. 18 de Julio 1246, Montevideo.
Secretary: Dr. Héctor Mourigan, Ave. 18 de Julio 2175, Montevideo.

NATIONAL

AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON PEDIATRICS

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Place: Atlantic City. Time: June 8-12, 1942.

AMERICAN ACADEMY OF PEDIATRICS

President: Dr. Edward C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Palmer House, Chicago. Time: Nov. 4-7, 1942.
Region I. Place: Bellevue-Stratford Hotel, Philadelphia. Time: April 1-3, 1942.
Region III. Place: Hotel Cleveland, Cleveland. Time: May 14-16, 1942.
Region IV. Meeting cancelled.

AMERICAN HOSPITAL ASSOCIATION, CHILDREN'S HOSPITAL SECTION

Chairman: Dr. D. L. Richardson, 593 Eddy St., Providence, R. I.
Secretary: Dr. Joelle C. Hiebert, 299 Main St. Lewiston, Maine.

AMERICAN PEDIATRIC SOCIETY

President: Dr. Edwards A. Park, Johns Hopkins Hospital, Baltimore, Md.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 30–May 2, 1942.

CANADIAN SOCIETY FOR THE STUDY OF DISEASES OF CHILDREN

President: Dr. L. M. Lindsay, 815 Medical Arts Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

SOCIETY FOR PEDIATRIC RESEARCH

President: Dr. George M. Guest, Children's Hospital, Cincinnati.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.
Place: Skytop Lodge, Skytop, Pa. Time: April 29-30, 1942.

SECTIONAL

INTERMOUNTAIN PEDIATRIC SOCIETY

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. R. Cannon Eley, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 319 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. S. G. Henricke, 4215 N. E. Hancock St., Portland, Ore.
Secretary: Dr. J. S. Backstrand, 333 Wyatt Court, Salem, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. Donn Barber, 802½–8th Ave., Greeley, Colo.
Secretary: Dr. Kenneth Schmidt, Republic Bldg., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. Harvey F. Garrison, 319 E. Capitol St., Jackson, Miss.
Secretary: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables, Fla.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. M. V. Adams, 803 Government St., Mobile.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William Belford, 233 A St., San Diego.
Secretary: Dr. John J. Miller Jr., 2398 Sacramento St., San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Warren W. Quillian, 227 Aragon Ave., Coral Gables.
Secretary: Dr. George N. Leonard, 605 Lincoln Rd., Miami Beach.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. R. C. McGahee, 1345 Greene St., Augusta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Ernest Caulfield, 683 Asylum Ave., Hartford.
Secretary: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.
Place: Springfield. Time: May 19-21, 1942.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Blvd., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. Julian Graubarth, 3431 Prytania St., New Orleans.
Secretary-Treasurer: Dr. W. C. Rivenbark, 3503 Prytania St., New Orleans.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Norman L. Hawkins, 11 Public Sq., Watertown, N. Y.
Secretary: Dr. William J. Orr, 135 Linwood Ave., Buffalo.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.
Secretary: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Place: Pittsburgh. Time: Sept. 29-Oct. 2, 1942.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Harry Towsley, University of Michigan Hospital, Ann Arbor.
Secretary: Dr. Leon DeVel, 110 E. Fulton, Grand Rapids.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. Andrew G. Dow, 314 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. John M. Thomas, 301 N. 49th St., Omaha.
Place: As announced by Committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW HAMPSHIRE PEDIATRIC SOCIETY

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. R. B. Josey, 1517 Hampton Ave., Columbia.
Secretary-Treasurer: Dr. Wilson Ball, South Carolina State Health Dept., Columbia.

TENNESSEE STATE PEDIATRIC SOCIETY

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Secretary: Dr. Gilbert Eblen, 611 W. Main Ave., Knoxville.

TEXAS PEDIATRIC SOCIETY

President: Dr. P. E. Luecke, 4105 Live Oak St., Dallas.
Secretary-Treasurer: Dr. John Ashby, 3610 Fairmount Ave., Dallas.

VIRGINIA PEDIATRIC SOCIETY

President: Dr. John M. Bishop, 511 Medical Arts Bldg., Roanoke.
Secretary: Dr. Edwin A. Harper, 301 Rivermont Ave., Lynchburg.

WEST VIRGINIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

President: Dr. Theresa O. Snaith, 450 Center Ave., Weston.
Secretary: Dr. Henrietta L. Marquis, 211 Bair Bldg., Beckley.

LOCAL

ACADEMY OF MEDICINE OF CLEVELAND, PEDIATRIC SECTION

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

ACADEMY OF MEDICINE, TORONTO, SECTION OF PEDIATRICS

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

BRONX PEDIATRIC SOCIETY

President: Dr. David Zahn, 2474 Valentine Ave., New York.
Secretary: Dr. Harry J. Cohen, 975 Walton Ave., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Paul L. Parrish, 52 S. Oxford St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank van der Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. James H. Wallace, 715 Lake St., Oak Park, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. Edgar Loomis, 351 W. Jefferson Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Marsh M. Poole, 773 Fisher Bldg., Detroit, Mich.
Secretary: Dr. Donald J. Barnes, 773 Fisher Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St. N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. John Aull, 1103 Grand Ave., Kansas City.
Secretary: Dr. George Herrmann, 1107 Bryant Bldg., Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Alonzo Cass, 1908 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Gladys Patric Shahovitch, 3936 Roderick Rd., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sydney Nussbaum, 247 Ocean View Ave., Brooklyn.
Secretary: Dr. Harry S. Bikoff, 850 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. A. A. Trivilino, 88-07–150th St., Jamaica, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. James M. Moser, 3751 Jenifer St. N. W., Washington, D. C.
Secretary-Treasurer: Dr. William A. Howard, 2222 Que St. N. W., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. E. C. Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Alfred Langmann, 108 E. 68th St., New York.
Secretary: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. John M. Adams, 1009 Nicollet Ave., Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. J. Byron Snow, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Place: Oklahoma Club. Time: Fourth Friday of each alternate month.

Philadelphia Pediatric Society

President: Dr. Philip S. Barda, 222 W. Harvey St., Germantown, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. E. L. Piper, 3200–5th Ave., Pittsburgh.
Secretary-Treasurer: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: I . Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Herman W. Farber, 501 E. Franklin St., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Maurice J. Lonsway, 3720 Washington Blvd., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from October to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Donald C. Shelby, 3780 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.
Time: Autumn, 1941.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.